To: Mickunas, Dave[Mickunas.Dave@epa.gov]; Humphrey, Marvelyn[humphrey.marvelyn@epa.gov]; Ritter, Melvin[Ritter.Melvin@epa.gov]
From: ONeill, Francis
Sent: Thur 12/17/2015 4:30:11 PM
Subject: A possible source for a 20 ppbv single component chloroprene standard.

I thought I would mention this lest we get off track. This exhausts my knowledge of possible suppliers of a 20 ppbv single compenent chloroprene standard.

Daniel Riemer, PhD

Apel-Riemer Environmental

Miami, Florida, USA

Phone: 786-925-6201

Fax: 786-364-1591

Ed

F. Edward O'Neill

US EPA Region 6 Houston Lab

281-983-2181

To: Stenger, Wren[stenger.wren@epa.gov]
From: Verhalen, Frances
Sent: Tue 12/8/2015 4:56:14 PM
Subject: RE: Chloroprene

Wren,

I suspect that you have received this information by now: Lady of Grace private school and Fifth Ward Elementary School. (These are listed in the action plan.)

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

From: Stenger, Wren
Sent: Monday, December 07, 2015 9:22 AM
To: Verhalen, Frances
Subject: Chloroprene

Need names of schools closest to DuPont.

Sent from my Windows Phone

To: Stenger, Wren[stenger.wren@epa.gov]; Verhalen, Frances[verhalen.frances@epa.gov]
From: Hansen, Mark
Sent: Mon 12/14/2015 6:00:22 PM
Subject: RE: Chloroprene

I believe the nearest other source is in Ascension Parish. Ruben confirmed.

From: Stenger, Wren
Sent: Monday, December 14, 2015 11:49 AM
To: Hansen, Mark; Verhalen, Frances
Subject: Chloroprene

Is Dupont the only facility with chloroprene discharges in St John?

Sent from my Windows Phone

To: Hansen, Mark[Hansen.Mark@epa.gov]; Verhalen, Frances[verhalen.frances@epa.gov]; Casso, Ruben[Casso.Ruben@epa.gov]
From: Stenger, Wren
Sent: Tue 12/1/2015 11:37:04 PM
Subject: FW: EJSCREEN - Dupont Pontchartrain Works - LAPLACE, LA
Dupont Pontchartrain Works ejscreen .5 mile Radius.pdf
ATT00001.htm
Dupont Pontchartrain Works ejscreen - 1 mile Radius.pdf
ATT00002.htm
Dupont Pontchartrain Works ejscreen - 3 mile Radius.pdf
ATT00003.htm

Wren Stenger

Director

Multimedia Planning and Permitting Division

EPA Region 6 Dallas, Texas

214.665.6583

From: Blanco, Arturo
Sent: Tuesday, December 01, 2015 3:32 PM
To: Coleman, Sam; Gray, David; Stenger, Wren; Blevins, John
Subject: FW: EJSCREEN - Dupont Pontchartrain Works - LAPLACE, LA

fyi

Arturo J. Blanco
Director

Office of Environmental Justice, Tribal and International Affairs

US EPA Region 6

1445 Ross Avenue (6RA-DA)

Dallas, TX 75202

214.665.3182 (o)

Ex. 6 - Personal Privacy (m)

From: Anderson, Israel
Sent: Tuesday, December 01, 2015 2:08 PM
To: Blanco, Arturo; Smith, Rhonda
Subject: Fwd: EJSCREEN - Dupont Pontchartrain Works - LAPLACE, LA

Here is EJSCREEN data.

Sent from my iPhone

Begin forwarded message:

From: "Runnels, Charlotte" <Runnels.Charlotte@epa.gov>
Date: December 1, 2015 at 1:13:59 PM CST
To: "Anderson, Israel" <Anderson.Israel@epa.gov>
Subject: EJSCREEN - Dupont Pontchartrain Works - LAPLACE, LA

Israel,

Attached are EJSCREEN Reports for Dupont Pontchartrain Works within a 5 mile, 1 mile and 3 mile radius of the facility.

To locate the address of the facility, I used the longitude and latitude from the ECHO database. See link below. http://echo.epa.gov/detailed-facility-report?fid=110000597131

To: Hansen, Mark[Hansen.Mark@epa.gov]; Verhalen, Frances[verhalen.frances@epa.gov]
From: Stenger, Wren
Sent: Mon 12/14/2015 5:49:09 PM
Subject: Chloroprene

Is Dupont the only facility with chloroprene discharges in St John?

Sent from my Windows Phone

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Casso, Ruben
Sent: Mon 10/19/2015 1:04:41 PM
Subject: FW: DuPont Follow up on chloroprene modeling and additional questions

From: PATRICK.A.WALSH@dupont.com [mailto:PATRICK.A.WALSH@dupont.com]
Sent: Thursday, October 15, 2015 5:28 PM
To: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Morris, Mark; Casso, Ruben; Rimer, Kelly; Strum, Madeleine
Subject: RE: Follow up on chloroprene modeling and additional questions
Importance: High

All,

I have reviewed all the appropriate information and my position hasn´t changed. I´m worried that EPA is going down the wrong path. Let me explain my thinking to you:

My problem is that the data as presented by EPA with regard to NATA are presented as "cancer risk":

Facility ID	FIPS	Tribal Code	Parameter	Pollutant	Risk Value (cancer risk reported in a million)	Facility Emissions (tpy)	Facility Name	State	County Name
80266	22095		Cancer risk	Chloroprene	16.04	0.0775	E I DuPont de Nemours & Co - Pontchartrain Site	LA	St. John the Baptist

(Taken from email from Madeleine Strum to Kelly Petersen, 6/24/15)

That would read to most people that chloroprene is a known, proven human carcinogen. But it hasn´t been proven, or even generally accepted, and EPA´s own toxicology data states such.

The IRIS database for chloroprene reads similarly to the IARC monograph:

"Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is evidence that chloroprene is ´likely to be carcinogenic to humans´"

Even the IRIS group will not explicitly state that chloroprene is a KNOWN human carcinogen. The entire series of documents discusses chloroprene´s carcinogenicity in mice and rats **only**. While they can be used as models for human physiology, mice and rats are NOT human, and there are numerous examples of materials that are spectacularly toxic to non-human animals but have little or no effect on humans (chocolate springs to mind). Therefore, it is, in my opinion, an irresponsibly large leap to present the chloroprene release data as definitely carcinogenic to humans by presenting it as "increased cancer risk".

In addition, the epidemiological data does not comport with the model at all. The following table describes actual cancer rates for St. John Parish for the most recent 4-year period for which data is available:

Rank	County	Annual Incidence Rate(†) over rate period - cases per 100,000	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Average Annual Count over rate period	Rate Period	Recent Trend	Recent 5-Year Trend (‡) in Incidence Rates	Lower 95% Confidence Interval	Upper 95% Confidence Interva
53	St. John the Baptist Parish(7,9)	460.8	432.3	490.7	209	2008-2012	stable	-2.2	-9.4	5.6

(Data from http://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&ag

Given the following:

1. 50+ year history making chloroprene in St. John Parish

2. 20-30 year latency period for most cancers

According to the risk factors EPA attributes to our chloroprene emissions, St. John Parish should have the highest cancer rate in the state. This should be especially true given that our history of emitting chloroprene is much longer than the typical latency for cancer. But in actuality, St. John is in the **lowest quartile** of measured cancer rates in the state (#53 out of 66 parishes) and the rate of cancer is decreasing according to the 5-year trend. Thus, the model has a serious flaw as it doesn´t come close to reflecting real, published cancer rate data.

The above, taken together, indicate that EPA is planning to publish misleading data in an inflammatory way. Therefore, it would be irresponsible to publish it. I strongly urge EPA to reconsider its present course.

Patrick A. Walsh, CIH

E.I. DuPont De Nemours and Company

Safety, Health, Environmental, and PSM Manager

DuPont Performance Polymers Pontchartrain Works

LaPlace, LA 70068

(985) 536-5731 Work

Ex. 6 - Personal Privacy Mobile

Patrick.A.Walsh@dupont.com

-----Original Appointment-----
From: Kelly Petersen [mailto:Kelly.Petersen@LA.GOV]
Sent: Tuesday, October 06, 2015 10:09 AM
To: Kelly Petersen; GREGO, DORIS B; ALLEN, JAMES B; SALDANA, CARLOS F; Palma, Ted; Morris, Mark; Casso, Ruben; 'Rimer, Kelly'; Strum, Madeleine; WALSH, PATRICK A.
Subject: Follow up on chloroprene modeling and additional questions
When: Tuesday, October 06, 2015 11:00 AM-12:00 PM (UTC-06:00) Central Time (US & Canada).
Where: `DEQ/Room 919 - OMF Conference

Please join a conference call at 11am central time on Tuesday, October 6th. The call in information is below.

Meeting Number Ex. 6 - Personal Privacy

To join the conference call:

Ex. 6 - Personal Privacy or international calls.

(2) Enter the Meeting Number, then #

Thanks, Kelly Petersen

Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

http://www.DuPont.com/corp/email_disclaimer.html

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Casso, Ruben
Sent: Mon 10/5/2015 2:35:16 PM
Subject: Conf call : Follow up on NATA chloroprene modeling and additional questions

Required: Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted <Palma.Ted@epa.gov>; Morris, Mark <Morris.Mark@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>; Strum, Madeleine <Strum.Madeleine@epa.gov>; PATRICK.A.WALSH@dupont.com

Please join a conference call at 11am central time on Tuesday, October 6th. The call in information is below.

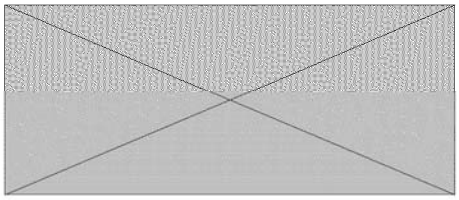
Meeting Number: Ex. 6 - Personal Privacy

To join the conference call:
(1) Dial Ex. 6 - Personal Privacy for international calls.
(2) Enter the Meeting Number, then #

Thanks, Kelly Petersen

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Jorge Lavastida
Sent: Tue 12/29/2015 7:34:21 PM
Subject: RE: Denka/DuPont Plant History
removed.txt

Thank you. Happy New Year to you also.



Jorge Lavastida, Executive Officer & Plant Manager

Denka Performance Elastomer LLC

560 Highway 44 | LaPlace, LA 70068

Office: 985-536-5466 | Cell: Ex. 6 - Personal Privacy

jorge-lavastida@denka-pe.com

From: Verhalen, Frances [mailto:verhalen.frances@epa.gov]
Sent: Tuesday, December 29, 2015 1:33 PM
To: Jorge Lavastida <Jorge-Lavastida@denka-pe.com>
Subject: RE: Denka/DuPont Plant History

Jorge, thank you for the prompt response.

First, next week is fine. Please let me know if you will be delayed past next Friday (Jan. 8). It is a holiday period and I truly understand. I, too, have many staff taking leave to be with family and friends.

Second, I expect that the production totals and timelines will work well. If not, I will contact you again.

I wish you a great (and safe) New Year.

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

From: Jorge Lavastida [mailto:Jorge-Lavastida@denka-pe.com]
Sent: Tuesday, December 29, 2015 1:27 PM
To: Verhalen, Frances
Subject: RE: Denka/DuPont Plant History

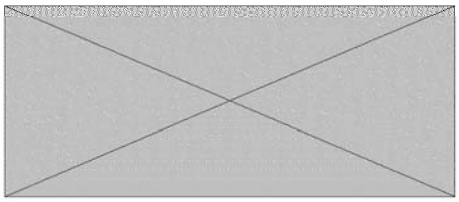
Fran,

I have forwarded this request to two personnel in my organization. With the New year holiday and one of them being on vacation this week it may be next week before we can submit the response. Hopefully that is Ok with you.

Will production totals and a timeline of the TN and LA facility history during the timeframe you cite address your questions?

Thanks,

Jorge



Jorge Lavastida, Executive Officer & Plant Manager

Denka Performance Elastomer LLC

560 Highway 44 | LaPlace, LA 70068

Office: 985-536-5466 | Cell: Ex. 6 - Personal Privacy

jorge-lavastida@denka-pe.com

From: Verhalen, Frances [mailto:verhalen.frances@epa.gov]
Sent: Tuesday, December 29, 2015 1:19 PM
To: Jorge Lavastida <Jorge-Lavastida@denka-pe.com>
Subject: Denka/DuPont Plant History

Jorge,

In reviewing the EI data for this time period, there is an observable dip in reported chloroprene emissions from 2006 to 2009 and then an increase in 2010. In that same time period, it is my understanding that DuPont's chloroprene plant in TN closed and the LA facility absorbed the work.

Can you provide me with some background and history of operations at the La Place, LA facility from 2006-2010 that can provide explanation for the drop in emissions and absorption of the TN work?

Many thanks.

Fran

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

From: Verhalen, Frances
Importance: Normal
Subject: Chloroprene call - Dupont
Start Date/Time: Tue 10/6/2015 4:00:00 PM
End Date/Time: Tue 10/6/2015 5:00:00 PM

Required: Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted <Palma.Ted@epa.gov>; Morris, Mark <Morris.Mark@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>; Strum, Madeleine <Strum.Madeleine@epa.gov>; PATRICK.A.WALSH@dupont.com

Please join a conference call at 11am central time on Tuesday, October 6th. The call in information is below.

Meeting Number: Ex. 6 - Personal Privacy

To join the conference call:
(1) Dial Ex. 6 - Personal Privacy for international calls.
(2) Enter the Meeting Number, then #

Thanks, Kelly Petersen

To: Jorge Lavastida[Jorge-Lavastida@denka-pe.com]
From: Verhalen, Frances
Sent: Tue 12/29/2015 7:32:42 PM
Subject: RE: Denka/DuPont Plant History

Jorge, thank you for the prompt response.

First, next week is fine. Please let me know if you will be delayed past next Friday (Jan. 8). It is a holiday period and I truly understand. I, too, have many staff taking leave to be with family and friends.

Second, I expect that the production totals and timelines will work well. If not, I will contact you again.

I wish you a great (and safe) New Year.

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

From: Jorge Lavastida [mailto:Jorge-Lavastida@denka-pe.com]
Sent: Tuesday, December 29, 2015 1:27 PM
To: Verhalen, Frances
Subject: RE: Denka/DuPont Plant History

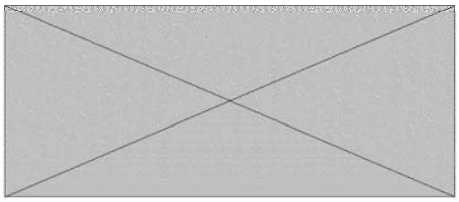
Fran,

I have forwarded this request to two personnel in my organization. With the New year holiday and one of them being on vacation this week it may be next week before we can submit the response. Hopefully that is Ok with you.

Will production totals and a timeline of the TN and LA facility history during the timeframe you cite address your questions?

Thanks,

Jorge



Jorge Lavastida, Executive Officer & Plant Manager

Denka Performance Elastomer LLC

560 Highway 44 | LaPlace, LA 70068

Office: 985-536-5466 | Cell: Ex. 6 - Personal Privacy

jorge-lavastida@denka-pe.com

From: Verhalen, Frances [mailto:verhalen.frances@epa.gov]
Sent: Tuesday, December 29, 2015 1:19 PM
To: Jorge Lavastida <Jorge-Lavastida@denka-pe.com>
Subject: Denka/DuPont Plant History

Jorge,

In reviewing the EI data for this time period, there is an observable dip in reported chloroprene emissions from 2006 to 2009 and then an increase in 2010. In that same time period, it is my understanding that DuPont's chloroprene plant in TN closed and the LA facility absorbed the work.

Can you provide me with some background and history of operations at the La Place, LA facility from 2006-2010 that can provide explanation for the drop in emissions and absorption of the TN work?

Many thanks.

Fran

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

To: Hansen, Mark[Hansen.Mark@epa.gov]; Stenger, Wren[stenger.wren@epa.gov]
Cc: Verhalen, Frances[verhalen.frances@epa.gov]
From: Casso, Ruben
Sent: Thur 12/17/2015 3:57:25 PM
Subject: Contact list for Dupont/Denka
EPA Region 6 contacts.docx

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Casso, Ruben
Sent: Thur 10/1/2015 8:34:56 PM
Subject: FW: follow up on chloroprene modeling and additional questions - Call with LDEQ/R6/OAQPS

From: Kelly Petersen [mailto:Kelly.Petersen@LA.GOV]
Sent: Thursday, October 01, 2015 3:26 PM
To: Rimer, Kelly; Strum, Madeleine; PATRICK.A.WALSH@dupont.com
Cc: Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Morris, Mark; Casso, Ruben; Amanda Polito; Vivian Aucoin; Maureen Fleming (DEQ)
Subject: RE: follow up on chloroprene modeling and additional questions

I would be happy to help set up a conference. I will be unavailable all day Wednesday next week.

Are any of the following times agreeable to everyone?

Monday, October 5 9-10am central

Tuesday, October 6 1-2pm central

Thursday, October 8 10-11am central

These are just suggested times, feel free to suggest an alternative if none of these work for you.

I will schedule a conference line and provide the connection information as soon as we have a time set. Do you need it to be a webinar or just a telephone conference?

Thanks,

Kelly Petersen

Air Permits Division

Louisiana Department of Environmental Quality

Phone: (225) 219-3397 Fax: (225) 325-8141 kelly.petersen@la.gov

From: Rimer, Kelly [mailto:Rimer.Kelly@epa.gov]
Sent: Thursday, October 01, 2015 2:52 PM
To: Strum, Madeleine; PATRICK.A.WALSH@dupont.com
Cc: Kelly Petersen; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Morris, Mark; Casso, Ruben
Subject: RE: follow up on chloroprene modeling and additional questions

Hi Patrick,

My name is Kelly Rimer and I am one of the managers overseeing the NATA analysis.

Thanks for your email. I think the next step is to set up a call where we can discuss the issue in depth. We will work with Kelly Petersen to set something up as soon as possible, hopefully next week.

Thanks,

Kelly Rimer

Leader, Air Toxics Assessment Group

US EPA

Office of Air Quality Planning and Standards

109 TW Alexander Drive

RTP. NC 27709

919-541-5368

From: Strum, Madeleine
Sent: Tuesday, September 29, 2015 2:20 PM
To: PATRICK.A.WALSH@dupont.com
Cc: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Rimer, Kelly; Morris, Mark; Casso, Ruben
Subject: RE: follow up on chloroprene modeling and additional questions

Hi Patrick,

Thanks for the below information. I'm going to pass this to the risk assessment group. Do you have information regarding emission estimation methods that I asked about below?

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

From: PATRICK.A.WALSH@dupont.com [mailto:PATRICK.A.WALSH@dupont.com]
Sent: Tuesday, September 29, 2015 2:14 PM
To: Strum, Madeleine
Cc: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com
Subject: FW: follow up on chloroprene modeling and additional questions

Hello Madeleine,

My name is Patrick Walsh and I am the Occupational Hygiene lead for the Neoprene side of the DuPont Pontchartrain site. Doris has kept me informed of your requests for information and we are, as always, happy to meet your needs. I've been doing some research, however, and I'm concerned about what EPA intends to do with this data.

Based on the various communications, it appears that EPA intends to publish their assertion that the amount of chloroprene we emit causes a substantially increased cancer risk in the surrounding area. I do not feel this is appropriate because the International Agency for Research on Cancer (IARC), generally considered in the OH profession as the final say of whether or not a material causes cancer, states that:

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to chloroprene has been

examined in two well conducted studies, one in the United States and one in Russia.

These investigations do not indicate a consistent excess of cancer at any site.

They then go on to state:

5.5 Evaluation

There is inadequate evidence in humans for the carcinogenicity of chloroprene. There is sufficient evidence in experimental animals for the carcinogenicity of chloroprene.

Overall evaluation

Chloroprene is possibly carcinogenic to humans (Group 2B).

The IARC monograph can be found here:

http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-9.pdf

The IARC study references many of the same documents discussed in chloroprene's IRIS database entry. Given this information, I think it is inappropriate to suggest that the low-level environmental exposure to chloroprene causes increased cancer risk. I request that the data reporting be adjusted to reflect this.

Please contact me with further questions, if any, at your convenience.

Patrick A. Walsh, CIH

E.I. DuPont De Nemours and Company

Safety, Health, Environmental, and PSM Manager

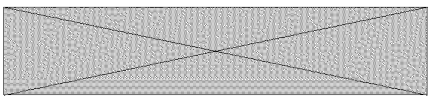
DuPont Performance Polymers Pontchartrain Works

LaPlace, LA 70068

(985) 536-5731 Work

Ex. 6 - Personal Privacy Mobile

Patrick.A.Walsh@dupont.com



From: GREGO, DORIS B
Sent: Monday, September 28, 2015 7:31 AM
To: WALSH, PATRICK A.
Subject: FW: follow up on chloroprene modeling and additional questions

FYI, EPA is asking for additional information for the Chloroprene Modeling.

Doris

From: Strum, Madeleine [mailto:Strum.Madeleine@epa.gov]
Sent: Thursday, September 24, 2015 11:06 AM
To: Kelly.Petersen@LA.gov; GREGO, DORIS B
Cc: Casso, Ruben; Thurman, James
Subject: follow up on chloroprene modeling and additional questions

Hi Kelly and Doris,

Thanks to Doris for providing the more detailed release information on the fans for the chloroprene releases at the DuPont facility. This is to follow up on the modeling James Thurman did using the updated information, and to ask follow up questions. The updated data allowed us to treat the fan releases as volume sources as opposed to the one large area source for 15.8 tons from process "PR0185". We found it didn't have a large impact on the results. Let me know if you'd like to see the updated modeling file spreadsheet with all of the revisions Doris provided.

My follow up questions are:

1. Kelly reported several emission estimation methods for the various different chloroprene sources. Among the highest chloroprene processes, the method of estimation are:

3 Other Emission Factor (pre-control) plus Control Efficiency

13	Other Emission Factor (no Control Efficiency used)	use if source and Emission Factor are uncontrolled or if Emission Factor itself accounts for controls without need to apply a control efficiency in emissions calculation
24	Stack Test (pre-control) plus Control Efficiency	use if test was before controls and therefore a control efficiency was also used in emissions calculation

Can you verify these methods? – What was the basis for the "Other Emission Factor" (33 and 13)– how was it determined—was there an initial test and an emission factor was determined for that?

2. A detailed spreadsheet showing the emissions calculation method by unit/process/method is attached. 77 tons (see totals at the bottom) use "13 (Other Emission Factor (no Control Efficiency used))" Does this mean the emissions are uncontrolled or do you have an emission factor that includes the impact of the condensers?

How did you determine the Control efficiency of the condenser(s) and what is it?

Do you have/can you send documentation of the emission calculations?

3. Are the condensers used for chloroprene recovery or is used just for emissions control?

Thanks much, and let me know if you would prefer to discuss this on a conference call than through email.

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Jorge Lavastida
Sent: Tue 12/29/2015 7:27:16 PM
Subject: RE: Denka/DuPont Plant History
removed.txt

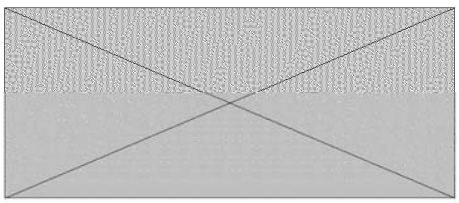
Fran,

I have forwarded this request to two personnel in my organization. With the New year holiday and one of them being on vacation this week it may be next week before we can submit the response. Hopefully that is Ok with you.

Will production totals and a timeline of the TN and LA facility history during the timeframe you cite address your questions?

Thanks,

Jorge



Jorge Lavastida, Executive Officer & Plant Manager

Denka Performance Elastomer LLC

560 Highway 44 | LaPlace, LA 70068

Office: 985-536-5466 | Cell: Ex. 6 - Personal Privacy

jorge-lavastida@denka-pe.com

From: Verhalen, Frances [mailto:verhalen.frances@epa.gov]
Sent: Tuesday, December 29, 2015 1:19 PM

To: Jorge Lavastida <Jorge-Lavastida@denka-pe.com>
Subject: Denka/DuPont Plant History

Jorge,

In reviewing the EI data for this time period, there is an observable dip in reported chloroprene emissions from 2006 to 2009 and then an increase in 2010. In that same time period, it is my understanding that DuPont's chloroprene plant in TN closed and the LA facility absorbed the work.

Can you provide me with some background and history of operations at the La Place, LA facility from 2006-2010 that can provide explanation for the drop in emissions and absorption of the TN work?

Many thanks.

Fran

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

To: Verhalen, Frances[verhalen.frances@epa.gov]; Robinson, Jeffrey[Robinson.Jeffrey@epa.gov]
From: Hansen, Mark
Sent: Mon 12/7/2015 7:00:33 PM
Subject: FW: DUPONT Information
Dupont Pontchartrain Works ejscreen .5 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 1 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 3 mile Radius.pdf
Dupont - Schools, Community Org, Faith Based Org - 2015.docx

FYI

From: Anderson, Israel
Sent: Monday, December 07, 2015 11:22 AM
To: Stenger, Wren; Blanco, Arturo; Blevins, John; Gilrein, Stephen; Yurk, Jeffrey; Smith, Rhonda; Edlund, Carl; Phillips, Pam; Seager, Cheryl; Hansen, Mark; Pettigrew, George; Honker, William; Garcia, David; Casso, Ruben; Harrison, Ben; Coleman, Sam; Johnson, Lydia; Runnels, Charlotte; Ruhl, Christopher; Lyke, Jennifer
Cc: Verhalen, Frances; Ruiz, Thomas; Crossland, Ronnie; McGee, Tomika; Young, Carl
Subject: FW: DUPONT Information

Resending EJSCREEN Reports for the .5 mile, 1 mile, and 3 mile radius from the DuPont Pontchartrain Works facility as well as some information about the two closest schools to the site and a list of community/environmental justice organizations who would need to be contacted when it is deemed appropriate and some info on nearby churches.

From: Runnels, Charlotte
Sent: Monday, December 07, 2015 11:00 AM
To: Anderson, Israel
Subject: DUPONT Information

To: Verhalen, Frances[verhalen.frances@epa.gov]
From: Casso, Ruben
Sent: Thur 10/1/2015 8:34:27 PM
Subject: FW: follow up on chloroprene modeling and additional questions

From: Strum, Madeleine
Sent: Thursday, October 01, 2015 3:31 PM
To: Kelly.Petersen@LA.gov
Cc: Rimer, Kelly; PATRICK.A.WALSH@dupont.com; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Morris, Mark; Casso, Ruben
Subject: RE: follow up on chloroprene modeling and additional questions

Hi Kelly Peterson,

Here are the available times for K. Rimer, T. Palma and R. Casso at EPA for next week based on the Outlook Scheduler.

1) Tuesday oct 6 between noon and 1pm Eastern (11am your time)

2) Thursday oct 8 between 10:15 and 11am pm Eastern (9:15 am your time)

3) Possibly Tuesday Oct 6, 2:30-3 Eastern (R. Casso looks like he might have something tentative)

Looks like K. Rimer is out Monday and K. Peterson is out Wednesday.

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

From: Rimer, Kelly
Sent: Thursday, October 01, 2015 3:52 PM
To: Strum, Madeleine; PATRICK.A.WALSH@dupont.com
Cc: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Morris, Mark; Casso, Ruben
Subject: RE: follow up on chloroprene modeling and additional questions

Hi Patrick,

My name is Kelly Rimer and I am one of the managers overseeing the NATA analysis.

Thanks for your email. I think the next step is to set up a call where we can discuss the issue in depth. We will work with Kelly Petersen to set something up as soon as possible, hopefully next week.

Thanks,

Kelly Rimer

Leader, Air Toxics Assessment Group

US EPA

Office of Air Quality Planning and Standards

109 TW Alexander Drive

RTP. NC 27709

919-541-5368

From: Strum, Madeleine
Sent: Tuesday, September 29, 2015 2:20 PM
To: PATRICK.A.WALSH@dupont.com
Cc: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com; Palma, Ted; Rimer, Kelly; Morris, Mark; Casso, Ruben
Subject: RE: follow up on chloroprene modeling and additional questions

Hi Patrick,

Thanks for the below information. I'm going to pass this to the risk assessment group. Do you have information regarding emission estimation methods that I asked about below?

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

From: PATRICK.A.WALSH@dupont.com [mailto:PATRICK.A.WALSH@dupont.com]
Sent: Tuesday, September 29, 2015 2:14 PM
To: Strum, Madeleine
Cc: Kelly.Petersen@LA.gov; Doris.B.Grego@dupont.com; James.B.Allen@dupont.com; Carlos.F.Saldana@dupont.com
Subject: FW: follow up on chloroprene modeling and additional questions

Hello Madeleine,

My name is Patrick Walsh and I am the Occupational Hygiene lead for the Neoprene side of the

DuPont Pontchartrain site. Doris has kept me informed of your requests for information and we are, as always, happy to meet your needs. I've been doing some research, however, and I'm concerned about what EPA intends to do with this data.

Based on the various communications, it appears that EPA intends to publish their assertion that the amount of chloroprene we emit causes a substantially increased cancer risk in the surrounding area. I do not feel this is appropriate because the International Agency for Research on Cancer (IARC), generally considered in the OH profession as the final say of whether or not a material causes cancer, states that:

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to chloroprene has been

examined in two well conducted studies, one in the United States and one in Russia.

These investigations do not indicate a consistent excess of cancer at any site.

They then go on to state:

5.5 Evaluation

There is inadequate evidence in humans for the carcinogenicity of chloroprene. There is sufficient evidence in experimental animals for the carcinogenicity of chloroprene.

Overall evaluation

Chloroprene is possibly carcinogenic to humans (Group 2B).

The IARC monograph can be found here:

http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-9.pdf

The IARC study references many of the same documents discussed in chloroprene's IRIS database entry. Given this information, I think it is inappropriate to suggest that the low-level environmental exposure to chloroprene causes increased cancer risk. I request that the data reporting be adjusted to reflect this.

Please contact me with further questions, if any, at your convenience.

Patrick A. Walsh, CIH

E.I. DuPont De Nemours and Company

Safety, Health, Environmental, and PSM Manager

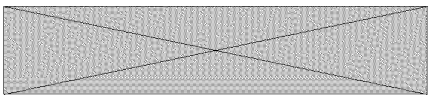
DuPont Performance Polymers Pontchartrain Works

LaPlace, LA 70068

(985) 536-5731 Work

Ex. 6 - Personal Privacy Mobile

Patrick.A.Walsh@dupont.com



From: GREGO, DORIS B
Sent: Monday, September 28, 2015 7:31 AM
To: WALSH, PATRICK A.
Subject: FW: follow up on chloroprene modeling and additional questions

FYI, EPA is asking for additional information for the Chloroprene Modeling.

Doris

From: Strum, Madeleine [mailto:Strum.Madeleine@epa.gov]
Sent: Thursday, September 24, 2015 11:06 AM
To: Kelly.Petersen@LA.gov; GREGO, DORIS B
Cc: Casso, Ruben; Thurman, James
Subject: follow up on chloroprene modeling and additional questions

Hi Kelly and Doris,

Thanks to Doris for providing the more detailed release information on the fans for the chloroprene releases at the DuPont facility. This is to follow up on the modeling James Thurman did using the updated information, and to ask follow up questions. The updated data allowed us to treat the fan releases as volume sources as opposed to the one large area source for 15.8 tons from process "PR0185". We found it didn't have a large impact on the results. Let me know if you'd like to see the updated modeling file spreadsheet with all of the revisions Doris provided.

My follow up questions are:

1. Kelly reported several emission estimation methods for the various different chloroprene sources. Among the highest chloroprene processes, the method of estimation are:

3 Other Emission Factor (pre-control) plus Control Efficiency

13	Other Emission Factor (no Control Efficiency used)	use if source and Emission Factor are uncontrolled or if Emission Factor itself accounts for controls without need to apply a control efficiency in emissions calculation
24	Stack Test (pre-control) plus Control Efficiency	use if test was before controls and therefore a control efficiency was also used in emissions calculation

Can you verify these methods? – What was the basis for the "Other Emission Factor" (33 and 13)– how was it determined—was there an initial test and an emission factor was determined for that?

2. A detailed spreadsheet showing the emissions calculation method by unit/process/method is attached. 77 tons (see totals at the bottom) use "13 (Other Emission Factor (no Control Efficiency used))" Does this mean the emissions are uncontrolled or do you have an emission factor that includes the impact of the condensers?

How did you determine the Control efficiency of the condenser(s) and what is it?

Do you have/can you send documentation of the emission calculations?

3. Are the condensers used for chloroprene recovery or is used just for emissions control?

Thanks much, and let me know if you would prefer to discuss this on a conference call than through email.

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

To: Jorge-lavastida@denka-pe.com[Jorge-lavastida@denka-pe.com]
From: Verhalen, Frances
Sent: Tue 12/29/2015 7:18:38 PM
Subject: Denka/DuPont Plant History

Jorge,

In reviewing the EI data for this time period, there is an observable dip in reported chloroprene emissions from 2006 to 2009 and then an increase in 2010. In that same time period, it is my understanding that DuPont's chloroprene plant in TN closed and the LA facility absorbed the work.

Can you provide me with some background and history of operations at the La Place, LA facility from 2006-2010 that can provide explanation for the drop in emissions and absorption of the TN work?

Many thanks.

Fran

Frances Verhalen, P.E., Chief

Air Monitoring and Grants Section

US Environmental Protection Agency

1445 Ross Avenue (MC 6MM-AM)

Dallas, TX 75202

214-665-2172

verhalen.frances@epa.gov

To: Anderson, Israel[Anderson.Israel@epa.gov]
From: Runnels, Charlotte
Sent: Mon 12/7/2015 5:00:27 PM
Subject: DUPONT Information
Dupont Pontchartrain Works ejscreen .5 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 1 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 3 mile Radius.pdf
Dupont - Schools, Community Org, Faith Based Org - 2015.docx

To: Runnels, Charlotte[Runnels.Charlotte@epa.gov]
From: Anderson, Israel
Sent: Wed 12/9/2015 10:54:25 PM
Subject: FW: DuPont Chloroprene
CDC -NIOSH Publication Chloroprene.pdf

From: Blanco, Arturo
Sent: Wednesday, December 09, 2015 4:34 PM
To: Anderson, Israel; Smith, Rhonda
Subject: FW: DuPont Chloroprene

Arturo J. Blanco
Director

Office of Environmental Justice, Tribal and International Affairs

US EPA Region 6

1445 Ross Avenue (6RA-DA)

Dallas, TX 75202

214.665.3182 (o)

Ex. 6 - Personal Privacy

From: Gray, David
Sent: Tuesday, December 08, 2015 7:20 AM
To: Stenger, Wren; Blanco, Arturo; Blevins, John; Seager, Cheryl; Edlund, Carl; Garcia, David;

Gilrein, Stephen; Harrison, Ben; Hill, Troy; Honker, William; McDonald, James; Phillips, Pam; Smith, Rhonda; Taheri, Diane; Luthans, William; Coleman, Sam; Curry, Ron
Subject: RE: DuPont Chloroprene

This information is from 1975 but interesting.

From: Stenger, Wren
Sent: Monday, December 07, 2015 6:00 PM
To: Blanco, Arturo; Blevins, John; Seager, Cheryl; Edlund, Carl; Garcia, David; Gilrein, Stephen; Gray, David; Harrison, Ben; Hill, Troy; Honker, William; McDonald, James; Phillips, Pam; Smith, Rhonda; Taheri, Diane; Luthans, William; Stenger, Wren; Coleman, Sam; Curry, Ron
Subject: DuPont Chloroprene

I am waiting for some additional information before I send the e file for another review. Hope to have it all by noon tomorrow. Will send separate note for the information still needed.

Wren Stenger

Director

Multimedia Planning and Permitting Division

EPA Region 6 Dallas, Texas

214.665.6583

To: Anderson, Israel[Anderson.Israel@epa.gov]
From: Runnels, Charlotte
Sent: Tue 12/1/2015 7:14:00 PM
Subject: EJSCREEN - Dupont Pontchartrain Works - LAPLACE, LA
Dupont Pontchartrain Works ejscreen .5 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 1 mile Radius.pdf
Dupont Pontchartrain Works ejscreen - 3 mile Radius.pdf

Israel,

Attached are EJSCREEN Reports for Dupont Pontchartrain Works within a 5 mile, 1 mile and 3 mile radius of the facility.

To locate the address of the facility, I used the longitude and latitude from the ECHO database. See link below. http://echo.epa.gov/detailed-facility-report?fid=110000597131

To: Blanco, Arturo[Blanco.Arturo@epa.gov]
From: Runnels, Charlotte
Sent: Fri 12/11/2015 9:40:33 PM
Subject: RE: Chloroprene DuPont NATA LDEQ/LDHH brief

Yes, can you send the latest information. Thanks

From: Blanco, Arturo
Sent: Friday, December 11, 2015 2:16 PM
To: Runnels, Charlotte
Subject: FW: Chloroprene DuPont NATA LDEQ/LDHH brief

Charlotte,

Please join me in this meeting. Thanks

Arturo

Arturo J. Blanco
Director

Office of Environmental Justice, Tribal and International Affairs

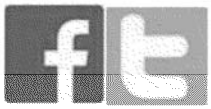
US EPA Region 6

1445 Ross Avenue (6RA-DA)

Dallas, TX 75202

214.665.3182 (o)

Ex. 6 - Personal Privacy m)



From: Stenger, Wren
Sent: Friday, December 11, 2015 12:31 PM
To: Gray, David; Coleman, Sam
Cc: Hansen, Mark; Williams, Odessa; Blanco, Arturo; Blevins, John; Seager, Cheryl; Edlund, Carl; Garcia, David; Gilrein, Stephen; Harrison, Ben; Hill, Troy; Honker, William; McDonald, James; Phillips, Pam; Smith, Rhonda; Taheri, Diane
Subject: Chloroprene DuPont NATA LDEQ/LDHH brief

David, for the call with LDEQ and LDHH on Monday, Dec 14 at 10 AM, my suggestion for those to be included on the invitation include:

Mike Koerber

Steve Page

Peter Tsirigotis

Penny Lassiter

Kelly Rhimer

Erika Sasser

Others from HQs? Millet, Jenny Noonan, Debbie Jordan, others???

George Pettigrew, Jennifer Lyke

Others from ATSDR or CDC?

Ron Curry, Sam Coleman, David Gray

Wren Stenger, Mark Hansen, Fran Verhalen, Ruben Casso

John Blevins, Steve Gilrein, Steve Thompson, Jeff Yurk

James McDonald, Troy Hill, Wes McQuiddy, Marvelyn Humphrey

Carl Edlund, Ronnie Crossland, Nick Fressia

Ben Harrison, Cheryl Seager

Arturo Blanco, Rhonda Smith, Israel Anderson

Others from R6?

LDEQ and LDHH will provide their names to you directly.

Wren Stenger

Director

Multimedia Planning and Permitting Division

EPA Region 6 Dallas, Texas

214.665.6583

From: Gray, David
Sent: Friday, December 11, 2015 11:56 AM
To: Tegan Treadaway; Stenger, Wren; Coleman, Sam; Noonan, Jenny
Subject: Re: NATA LDEQ/LDHH brief

We have the briefing set up for Monday at 10 am CT. We will need a list of attendees in advance of the meeting so they can access the webinar presentation.

Please send names to me and Jenny Noonan.

Below are details.

For this meeting with the Departments of Environment and Health for the State of Louisiana, we will be using the call in number Ex. 6 - Personal Privacy

To view the webinar, Ex. 6 - Personal Privacy

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Sent from my iPhone

On Dec 10, 2015, at 4:16 PM, Tegan Treadaway <Tegan.Treadaway@LA.GOV> wrote:

> If not/ please let us know what works. DHH is not available in the pm.
>
> Sent from my iPhone

To: Anderson, Israel[Anderson.Israel@epa.gov]
From: Runnels, Charlotte
Sent: Mon 12/7/2015 11:05:16 PM
Subject: LaPlace, Louisiana - Dupont Pontchartrain Works
Dupont - Schools, Community Org, Faith Based Org - 2015.docx

Israel,

See the attached chart with information on LaPlace, LA.

Charlotte

To: Blanco, Arturo[Blanco.Arturo@epa.gov]
From: Runnels, Charlotte
Sent: Fri 12/11/2015 9:18:08 PM
Subject: RE: Chloroprene DuPont NATA LDEQ/LDHH brief

Arturo,

This meeting is on my calendar for Monday.

From: Blanco, Arturo
Sent: Friday, December 11, 2015 2:16 PM
To: Runnels, Charlotte
Subject: FW: Chloroprene DuPont NATA LDEQ/LDHH brief

Charlotte,

Please join me in this meeting. Thanks

Arturo

Arturo J. Blanco
Director

Office of Environmental Justice, Tribal and International Affairs

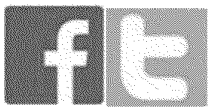
US EPA Region 6

1445 Ross Avenue (6RA-DA)

Dallas, TX 75202

214.665.3182 (o)

Ex. 6 - Personal Privacy (m)



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Sent: Friday, December 11, 2015 12:31 PM
To: Gray, David; Coleman, Sam
Cc: Hansen, Mark; Williams, Odessa; Blanco, Arturo; Blevins, John; Seager, Cheryl; Edlund, Carl; Garcia, David; Gilrein, Stephen; Harrison, Ben; Hill, Troy; Honker, William; McDonald, James; Phillips, Pam; Smith, Rhonda; Taheri, Diane
Subject: Chloroprene DuPont NATA LDEQ/LDHH brief

David, for the call with LDEQ and LDHH on Monday, Dec 14 at 10 AM, my suggestion for those to be included on the invitation include:

Mike Koerber

Steve Page

Peter Tsirigotis

Penny Lassiter

Kelly Rhimer

Erika Sasser

Others from HQs? Millet, Jenny Noonan, Debbie Jordan, others???

George Pettigrew, Jennifer Lyke

Others from ATSDR or CDC?

Ron Curry, Sam Coleman, David Gray

Wren Stenger, Mark Hansen, Fran Verhalen, Ruben Casso

John Blevins, Steve Gilrein, Steve Thompson, Jeff Yurk

James McDonald, Troy Hill, Wes McQuiddy, Marvelyn Humphrey

Carl Edlund, Ronnie Crossland, Nick Fressia

Ben Harrison, Cheryl Seager

Arturo Blanco, Rhonda Smith, Israel Anderson

Others from R6?

LDEQ and LDHH will provide their names to you directly.

Wren Stenger

Director

Multimedia Planning and Permitting Division

EPA Region 6 Dallas, Texas

214.665.6583

From: Gray, David
Sent: Friday, December 11, 2015 11:56 AM
To: Tegan Treadaway; Stenger, Wren; Coleman, Sam; Noonan, Jenny
Subject: Re: NATA LDEQ/LDHH brief

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> If not/ please let us know what works. DHH is not available in the pm.
>
> Sent from my iPhone

To: Runnels, Charlotte[Runnels.Charlotte@epa.gov]
From: Anderson, Israel
Sent: Mon 12/7/2015 10:54:34 PM
Subject: FW: DUPONT Information

Can you go to the web and pull a short paragraph on the La Place Community for me to send to her.

From: Stenger, Wren
Sent: Monday, December 07, 2015 4:46 PM
To: Anderson, Israel
Subject: RE: DUPONT Information

Can you send me a paragraph that describes the community for the action plan?

Wren Stenger

Director

Multimedia Planning and Permitting Division

EPA Region 6 Dallas, Texas

214.665.6583

From: Anderson, Israel
Sent: Monday, December 07, 2015 11:22 AM
To: Stenger, Wren; Blanco, Arturo; Blevins, John; Gilrein, Stephen; Yurk, Jeffrey; Smith, Rhonda; Edlund, Carl; Phillips, Pam; Seager, Cheryl; Hansen, Mark; Pettigrew, George; Honker, William; Garcia, David; Casso, Ruben; Harrison, Ben; Coleman, Sam; Johnson, Lydia; Runnels, Charlotte; Ruhl, Christopher; Lyke, Jennifer
Cc: Verhalen, Frances; Ruiz, Thomas; Crossland, Ronnie; McGee, Tomika; Young, Carl
Subject: FW: DUPONT Information

Resending EJSCREEN Reports for the .5 mile, 1 mile, and 3 mile radius from the DuPont Pontchartrain Works facility as well as some information about the two closest schools to the site and a list of community/environmental justice organizations who would need to be contacted when it is deemed appropriate and some info on nearby churches.

From: Runnels, Charlotte
Sent: Monday, December 07, 2015 11:00 AM
To: Anderson, Israel
Subject: DUPONT Information

From: Runnels, Charlotte
Importance: Normal
Subject: Chloroprene DuPont NATA LDEQ/LDHH brief
Start Date/Time: Mon 12/14/2015 4:00:00 PM
End Date/Time: Mon 12/14/2015 5:00:00 PM

Charlotte,

Please join me in this meeting. Thanks

Arturo

Arturo J. Blanco
Director
Office of Environmental Justice, Tribal and International Affairs
US EPA Region 6
1445 Ross Avenue (6RA-DA)
Dallas, TX 75202
214.665.3182 (o)
Ex. 6 - Personal Privacy

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Others from HQs? Millet, Jenny Noonan, Debbie Jordan, others???

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Ron Curry, Sam Coleman, David Gray
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Others from R6?

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Wren Stenger
Director
Multimedia Planning and Permitting Division
EPA Region 6 Dallas, Texas
214.665.6583

From: Gray, David
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If not/ please let us know what works. DHH is not available in the pm.

Sent from my iPhone

Chloroprene; CASRN: 126-99-8

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Chloroprene

File First On-Line 09/30/2010

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	message	09/30/2010
Inhalation RfC (I.B.)	yes	09/30/2010
Carcinogenicity Assessment (II.)	yes	09/30/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section I.A. Last Revised – 09/30/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of

substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous oral RfD for chloroprene on IRIS.

I.A.1. CHRONIC ORAL RfD SUMMARY

There are no human data involving oral exposure to chloroprene. The only lifetime oral study in animals exposed rats to chloroprene at one dose (50 mg/kg/day) and only qualitatively reported noncancer effects (Ponomarkov and Tomatis, 1980).

Critical Effect	Point of Departure	UF	Chronic RfD
No oral studies available	N/A	N/A	Not derived

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Not applicable

I.A.3. UNCERTAINTY FACTORS

Not applicable

I.A.4. ADDITIONAL STUDIES/COMMENTS

Not applicable

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Not applicable

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document – (U.S. EPA, 2010)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to the EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloropene* (U.S. EPA, 2009). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF).***

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section I.B. Last Revised – 09/30/2010

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. A summary of the evaluation of potential human carcinogenicity of chloroprene is contained in Section II of this file.

An inhalation assessment for chloroprene was not previously available on IRIS.

I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
Co-critical effects: increase in incidence of olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic proliferation in male F344/N rats, female F344/N rats, and female B6C3F$_1$ mice, respectively (NTP, 1998)	$BMDL_{HEC}$: 2 mg/m^3	100	2×10^{-2} mg/m^3

*Conversion Factors and Assumptions. For the purposes of deriving an RfC for chloroprene, effects observed in male and female rats and male and female mice were evaluated from the 2 year chronic study by NTP (1998, 042076). Due to the nature and severity of the nasal degenerative effects (i.e., olfactory atrophy and necrosis), and the proximity of the $BMDL_{10}$ values to the observed LOAEL compared to other endpoints (Table 5-2), a BMR of 5% was considered appropriate for these olfactory endpoints. The nature of the observed nasal lesions potentially included the loss of Bowman's glands and olfactory axons in more severe cases. Effects that occur in the underlying lamina propria and basal layer of the olfactory epithelium may be indicative of more marked nasal tissue injury. For all other endpoints, a BMR of 10% was chosen as the response level. For the endpoints - olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation - after rounding to one significant figure, the PODADJ resulted in a value of 2 mg/m^3, which was used as the POD for deriving the RfC (U.S. EPA, 1995, 005992; U.S. EPA, 2000, 052150). The POD_{HEC} or $BMDL_{HEC}$ was calculated by applying a DAF of 1.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

There is a limited body of information on the nonneoplastic toxicological consequences to humans who are exposed to chloroprene. Chloroprene has been reported to cause respiratory, eye, and skin irritation, chest pains, temporary hair loss, dizziness, insomnia, headache, and fatigue in occupationally exposed workers (Nystrom, 1948). Other effects reported include changes in the nervous system (lengthening of sensorimotor response to visual cues and increased olfactory thresholds), cardiovascular system (muffled heart sounds, reduced arterial pressure, and tachycardia), and hematological parameters (reduced RBC counts, decreased hemoglobin, erythrocytopenia, leucopenia, and thrombocytopenia) (Sanotskii, 1976).

In animals, toxicity in multiple organ systems, including respiratory tract, kidney, liver, spleen, and forestomach effects, was observed in short-term, subchronic, and chronic inhalation studies (NTP (1998)[also reported by Melnick et al. (1999) and Trochimowicz et al (1998)].

From the available chronic studies, the NTP (1998)study was chosen as the principal study for the derivation of the RfC. This study utilized 50 animals per sex, per exposure group, a range of exposure concentrations based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thoroughly examined chloroprene's observed toxicity in two species (Fischer rats and B6C3F_1 mice). Trochimowicz et al. (1998) was not chosen as the principal study due to concerns regarding high mortality observed in the low dose male and female rats due to the failure in the exposure chamber ventilation system. The high mortality in this dose group prevented histopathological examination of most organ systems (except for liver samples) and precluded any firm conclusions on dose-response characteristics from being drawn. Also, a lack of adverse effects at similar exposure levels as the NTP (1998) study (Trochimowicz et al. (1998); see Section 4.7.2.2 for discussion of potential causes of differences in observed toxicity between the NTP and Trochimowicz studies) was observed and influenced the choice to not select the Trochimowicz et al. (1998) as the principal study.

In the 2-year (NTP, 1998) inhalation study of chloroprene in male and female rats and mice, groups were exposed to target concentrations of 0, 12.8, 32, and 80 ppm chloroprene. Actual chamber concentrations achieved were 0, 12.8 ± 0.4, 31.7 ± 1.1, and 79.6 ± 1.6 and 0, 12.7 ± 0.4, 31.9 ± 0.9, and 79.7 ± 1.7 ppm chloroprene for rats and mice, respectively. All animals were observed twice daily, and body weights were recorded initially, weekly through week 12, approximately every 4 weeks from week 15 through week 91, and every 2 weeks until the end of the study. Clinical findings were recorded initially at weeks 4, 8, 12, and 15, every 4 weeks through week 91, and every 2 weeks until the end of the study. Complete necropsy and microscopic examinations were performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, liver, lung, lymph nodes (bronchial,

mandibular, mediastinal, and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. A LOAEL of 12.8 ppm was identified from this study based on the observation of nonneoplastic lesions in multiple organ systems in animals exposed to the lowest exposure concentration.

From the NTP (1998) study, all nonneoplastic lesions that were statistically increased in rats or mice at the low- or mid-exposure concentration (12.8 or 32 ppm) compared to chamber controls, or demonstrated a suggested dose-response relationship in the low- or mid-exposure range in the absence of statistical significance, were considered candidates for the critical effect. The candidate endpoints included: alveolar epithelial hyperplasia, olfactory chronic inflammation, olfactory necrosis, olfactory epithelium atrophy, olfactory basal cell hyperplasia, olfactory metaplasia, and kidney (renal tubule) hyperplasia in rats; and bronchiolar hyperplasia, olfactory suppurative inflammation, kidney (renal tubule) hyperplasia, forestomach epithelial hyperplasia, and splenic hematopoietic cell proliferation in mice.

Methods of Analysis. This assessment used benchmark dose (BMD) methodology, where possible, to estimate a POD for the derivation of an RfC for chloroprene. Data for some endpoints were not amenable to BMD modeling; therefore the NOAEL/LOAEL approach was used for these data. A BMR of 10% extra risk is typically chosen as a standard response level for dichotomous data and is recommended for the BMR when using dichotomous models to facilitate a consistent basis of comparison across assessments and endpoints (U.S. EPA, 2000). For the data from the NTP (1998) study, a BMR of 10% extra risk was used initially. In addition to the incidence of the endpoints, the NTP (1998) study also reported the severity scores for individual animals in each dose group, thus making it possible to determine whether the endpoints were increasing in severity as well as incidence with dose.

Due to the nature and severity of the nasal degenerative effects (i.e., olfactory atrophy and necrosis), and the proximity of the $BMDL_{10}$ values to the observed LOAEL compared to other endpoints (Table 5-2), a BMR of 5% was considered appropriate for these olfactory endpoints. The nature of the observed nasal lesions potentially included the loss of Bowman's glands and olfactory axons in more severe cases. Effects that occur in the underlying lamina propria and basal layer of the olfactory epithelium may be indicative of more marked nasal tissue injury. For all other endpoints, a BMR of 10% was chosen as the response level.

Using BMD modeling, duration and dosimetric adjustments, increased incidence of olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation in male F344/N rats, female F344/N rats, and female $B6C3F_1$ mice, respectively, were identified as co-critical

effects. For these endpoints the $BMDL_{HEC}$ resulted in a value of 2 mg/m^3, which was used as the point of departure for deriving the RfC.

I.B.3. UNCERTAINTY FACTORS

$UF = 100 = 3\ (UF_A) \times 10\ (UF_H) \times 1\ (UF_S) \times 1\ (UF_L) \times 3\ (UF_D)$

An UF of 3 ($10^{1/2} = 3.16$, rounded to 3) was applied for interspecies extrapolation (UF_A) to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). This uncertainty factor is comprised of two separate and equal areas of uncertainty to account for differences in the toxicokinetics and toxicodynamics of animals and humans. In this assessment, toxicokinetic uncertainty was accounted for by the calculation of a human equivalent concentration by the application of a dosimetric adjustment factor as outlined in the RfC methodology (U.S. EPA, 1994). As the toxicokinetic differences are thus accounted for, only the toxicodynamic uncertainties remain, and a UF of 3 is retained to account for this residual uncertainty.

An UF of 10 was applied to account for variation in susceptibility among members of the human population (i.e., interindividual variability; UF_H). Only limited information is available to assess potential variability in human susceptibility, such as data regarding the human variability in expression of enzymes involved in chloroprene metabolism (e.g., metabolic activation via p450 isoform CYP2E1) (Bernauer et al., 2003). No data is currently available on the toxicodynamic variability within the human population. Therefore, in accordance with EPA policy (U.S. EPA, 2002), the default 10-fold UF_H is applied and presumed to account for variations in susceptibility within the human population.

An UF_S was not needed to account for subchronic-to-chronic extrapolation because a chronic inhalation study is being used to derive the chronic RfC. An UF for LOAEL-to-NOAEL extrapolation was not applied because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 5% change in olfactory atrophy and a BMR of 10% change in alveolar hyperplasia and splenic hematopoietic cell proliferation was selected under an assumption that these BMR levels represent a minimal biologically significant change for these endpoints.

An UF of 3 was applied to account for deficiencies in the database. The major strength of the database is the observation of exposure-response effects in multiple organ systems in a well-designed chronic inhalation study that utilized 50 animals per sex per dose group, a range of doses based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thorough examination of the toxicity of chloroprene in two species (rat and mouse). The database further contains another chronic inhalation bioassay investigating outcomes in

another species (hamster), and well-designed embryotoxicity, teratological, and reproductive toxicity studies. The database also contains subchronic studies and chronic studies observing potential neurotoxic and immunotoxic effects. A limitation in the database is the lack of a full two-generation reproductive toxicity study (the Appelman and Dreef van der Meulen (1979) unpublished study exposed F_0 and F_1 rats to chloroprene, but did not allow the F_1 rats to mate).

I.B.4. ADDITIONAL STUDIES/COMMENTS

The results of BMD modeling indicated that olfactory atrophy in the male rat, alveolar hyperplasia in the female rat, and splenic hematopoietic cell proliferation in the female mouse were the most sensitive endpoints, with a POD_{ADJ} values of 2.3, 2.1, and 2.1 mg/m^3, respectively. For these endpoints, after rounding to one significant figure, the POD_{ADJ} resulted in a value of 2 mg/m^3,which was used as the point of departure for deriving the RfC.

Chloroprene is a relatively water-insoluble, nonreactive gas, with an approximate blood:air partition coefficient of less than 10 (see Table 3-1), that induces a range of nasal, thoracic, and systemic noncancer effects. Water-insoluble, nonreactive chemicals typically do not partition greatly into the aqueous mucus coating of the upper respiratory system. Rather, they tend to distribute to the lower portions of the respiratory tract where larger surface areas and the thin alveolar-capillary barrier facilitate uptake (Medinsky and Bond, 2001). The observation of systemic (i.e., nonrespiratory) effects resultant from chloroprene exposure clearly indicates the compound is absorbed into the bloodstream and distributed throughout the body. Further, the distribution of lesions (olfactory effects, but no respiratory mucosal damage) is indicative of a critical role for blood borne delivery and in situ metabolic activation. The absence of respiratory mucosal injury suggests that direct reactivity of the parent compound is not likely involved. Rather, the pattern of respiratory effects seen following chloroprene exposure is consistent with what is known about its metabolism and the expression of cytochrome P450 enzymes in the olfactory mucosa and lower respiratory tract in rats. The proposed mode of action of chloroprene involves the conversion of the parent compound into its reactive epoxide metabolite by P450 isoform CYP2E1. The olfactory mucosa of rats has been shown to specifically express CYP2E1 at levels more similar to hepatic levels than any other nonhepatic tissue examined (Thornton-Manning and Dahl, 1997). Himmelstein et al. (2004) observed that the microsomal fraction of rat lung homogenates was active in the metabolic oxidation of chloroprene into (1-chloroethenyl)oxirane at levels between 10-30% that of liver microsomes. *In situ* conversion of chloroprene into its highly reactive epoxide metabolite in the olfactory epithelia and lower respiratory tract may facilitate its uptake in these tissues and explain a portion of its biological activity in those regions. Evidence for metabolic activation in the respiratory tract combined with the observation that chloroprene induces effects in organ systems distal to the portal-of-entry, consistent with the parent compound's water-insoluble

and nonreactive chemical properties, suggest that chloroprene's principal mode of action does not involve direct reactivity of the parent compound at the portal of entry.

Consequently, the selected critical effects, olfactory atrophy, alveolar hyperplasia, and splenic hematopoietic cell proliferation, are assumed to primarily result from systemic distribution and the human equivalent concentration (HEC) for chloroprene was calculated by the application of the appropriate dosimetric adjustment factor (DAF) for category 3 gases (in this case 1 for systemic effects), in accordance with the U.S. EPA RfC methodology (U.S. EPA, 1994).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study – High
Database – Medium to High
RfC – Medium to High

Confidence in the principal study (NTP, 1998) is judged to be high as it was a well-designed study using two test species (rats and mice) with 50 animals per dose group. This study appropriately characterizes a range of chloroprene-induced nonneoplastic and neoplastic lesions, as determined by independent, external peer review. In addition, the key histopathological lesions observed are appropriately described, and suitable statistical analysis is applied to all animal data.

The co-critical noncancer effects, olfactory atrophy in the male rat, alveolar hyperplasia in the female rat, and splenic hematopoietic cell proliferation in the female mouse , is consistent with what is known about the metabolism and systemic distribution of chloroprene.

Confidence in the overall database specific to chloroprene is medium to high. The major strength of the database is the observation of dose-response effects in multiple organ systems in a well-designed chronic inhalation study that utilized 50 animals per sex per dose group, a range of doses based on the results of preliminary, shorter-duration studies (16 day and 13 weeks), and thorough examination of toxicity of chloroprene in two species (rat and mouse). The database further contains another chronic inhalation bioassay investigating outcomes in another species (hamster), and well-designed embryotoxicity, teratological, and reproductive toxicity studies. The database also contains subchronic studies and chronic studies observing potential neurotoxic and immunotoxic effects. A major limitation in the database is the lack of a complete two-generation reproductive toxicity study.

Therefore, confidence in the RfC is judged to be medium to high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – (U.S. EPA, 2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Chloroprene
CASRN – 126-99-8
Section II. Last Revised – 09/30/2010

This section provides information on the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005). The quantitative risk estimates are derived from the application of a low-

dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A cancer assessment for chloroprene was not previously available on IRIS.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is evidence that chloroprene is "*likely to be carcinogenic to humans*" based on: (1) statistically significant and dose-related information from an NTP (1998) chronic inhalation bioassay demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) the proposed mutagenic mode of action; and (5) structural similarities between chloroprene and known human carcinogens, butadiene and vinyl chloride.

According to NTP (1998), there is clear evidence of carcinogenicity in the F344/N rat and $B6C3F_1$ mouse due to lifetime inhalation exposure to chloroprene. In rats, increased incidences of neoplastic lesions primarily occurred in the oral cavity (both sexes), lung (males only), kidney (both sexes), and mammary gland (females). In mice, increased incidences in neoplasms occurred in the lungs (both sexes), circulatory system (all organs, both sexes), Harderian gland (both sexes), forestomach (both sexes), liver (females only), skin (females only), mammary gland (females only), and kidney (males only).

Among epidemiological studies investigating the association between cancer mortality and chloroprene exposure in eight occupational cohorts, four studies observed statistically significantly associations (i.e., two- to five-fold increased risk) between liver/biliary passage cancer cases and chloroprene exposure (Bulbulyan et al., 1998; Bulbulyan et al., 1999; Leet and Selevan, 1982; Li et al., 1989). An increased risk of lung cancer incidence and mortality was observed in a few studies (Bulbulyan et al., 1998; Colonna and Laydevant, 2001; Leonard et al., 2007; Li et al., 1989; Pell, 1978), although few statistically significant associations were reported.

Compelling evidence for the hypothesized mutagenic mode of action for chloroprene includes: 1) chloroprene, like butadiene and isoprene, is metabolized to epoxide intermediates (Bartsch et al., 1979; Cottrell et al., 2001; Himmelstein et al., 2001; Hurst and Ali, 2007); 2) chloroprene forms DNA adducts via its epoxide metabolite (Munter et al., 2007; Munter, et al., 2002), and is a point mutagen in vitro (in some but not all bacterial assays) and in vivo (Bartsch et al., 1979; Drevon and Kuroki, 1979; Foureman et al., 1994; Himmelstein et al., 2001; NTP, 1998; Shelby and Witt, 1995; Vogel, 1979; Westphal et al., 1994; Willems, 1978; Willems, 1980); 3) observation of the genetic alterations (base-pair transversions) in proto-oncogenes in chloroprene-induced lung, Harderian gland, and forestomach neoplasms in mice (NTP, 1998; Sills et al., 1999; Sills et al., 2001; Ton et al., 2007); and 4) similarities in tumor sites and sensitive species between chloroprene and butadiene in chronic rodent bioassays (NTP (1998) and Melnick et al. (1999), respectively).

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

A number of occupational cohort studies have examined cancer mortality and incidence among workers exposed to chloroprene monomer and/or polychloroprene latex in the United States, Russia (Moscow), Armenia, France, China, and Ireland (Bulbulyan et al., 1998; Bulbulyan et al., 1999; Colonna and Laydevant, 2001; Leet and Selevan, 1982; Li et al., 1989; Marsh et al., 2007; Marsh et al., 2007; Pell, 1978; Romazini et al., 1992).

Despite these differences in occupational exposure to chloroprene and other chemicals, four of the cohorts with observed liver/biliary passage cancer cases showed statistically significant associations (i.e., two- to five-fold increased risk) with chloroprene exposure. Four mortality studies reported SMRs of 339, 240, 242, 571 when compared to external populations (Bulbulyan et al., 1998; Bulbulyan et al., 1999; Leet and Selevan, 1982; Li et al., 1989). Although sample size and statistical power were limited (thus limiting the precision of risk estimates), Bulbulyan et al. (1998; 1999) observed significantly elevated relative risk estimates for liver cancer incidence and mortality among intermediate and highly exposed workers. The study involving four plants (including the Louisville Works plant included in the Leet and Selevan (1982) study) by Marsh et al. (2007), which had the largest sample size and most extensive exposure assessment, also observed increased relative risk estimates for liver cancer in relation to cumulative exposure in the plant with the highest exposure levels (trend p value = 0.09, RRs 1.0, 1.90, 5.10, and 3.33 across quartiles of exposure, based on 17

total cases). Although not statistically significant, these findings are consistent in magnitude with results (RR range: 2.9-7.1) detected in two other studies for high and intermediate cumulative exposures (Bulbulyan et al., 1998; Bulbulyan et al., 1999).

The EPA guidelines for carcinogen risk assessment (U.S. EPA, 2005) advocate the use of "criteria" proposed by Hill (1965) to assess causality. There exist a number of methodological limitations in the chloroprene epidemiologic studies that may preclude drawing firm conclusions regarding those criteria: lack of control of personal confounders and risk factors associated with the outcomes in question, imprecise exposure ascertainment resulting in crude exposure categories, incorrect enumeration of cases leading to misclassification errors, limited sample sizes, and the healthy worker effect. However, the temporality of exposure prior to occurrence of liver cancer, strength of association, consistency, suggestive biological gradient, and biological plausibility provide some evidence for carcinogenicity of chloroprene in humans.

II.A.3. ANIMAL CARCINOGENICITY DATA

There is clear evidence of carcinogenicity in the F344/N rat and B6C3F$_1$ mouse due to lifetime inhalation exposure to chloroprene (NTP, 1998). The mouse is regarded as the most sensitive species because tumor incidence and multisite distribution were greater than with the rat. There was decreased survival in chloroprene-exposed rats and mice, and survival in mice was significantly associated with the burden of neoplastic lesions. Mortality in rats was likely due to overt toxicity across many organ systems. In rats, statistically significantly increased incidences of neoplastic lesions occurred in the oral cavity (papillomas or carcinomas, males and females), kidney (renal tubule adenomas or carcinomas, males), thyroid gland (adenomas or carcinomas, males) and mammary gland (fibroadenomas, females). In mice, increased incidences in neoplasms occurred in the lungs (adenomas or carcinomas, males and females), circulatory system (hemangiomas or hemangiosarcomas, all organs, males and females), Harderian gland (adenomas or carcinomas, males and females), liver (adenomas or carcinomas, females), skin and mesentery (sarcomas, females), mammary gland (carcinomas, females), and kidney (renal tubule adenomas or carcinomas, males). The observation of that chloroprene is more potent in inducing tumors in B6C3F$_1$ mice compared to F344/N rats may be due to species differences in metabolism. The activity of liver or lung microsomal oxidation of chloroprene and the formation of (1-chlorocthenyl)oxirane was higher in the mouse than the rat (Himmelstein et al. (2004). Additionally, the activity of epoxide hydrolase in liver microsomes was greater in the rat compared to the mouse (epoxide hydrolase activity was approximately equal in lung microsomes). The observation that formation of the reactive epoxide metabolite of chloroprene is greatest in the mouse lung may explain the observation that chloroprene exposure induces lung tumors in mice, but not rats.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The inhalation study by Dong et al. (1989) found that a 7-month exposure of the Kunming strain of albino mice, a strain reported to have a low spontaneous rate of lung tumor formation, resulted in a chloroprene-associated increase in lung tumors. Although quality assurance procedures regarding histopathology were not reported, these study results are considered to support the findings in the $B6C3F_1$ mice in the NTP (1998) chronic bioassay.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. ORAL SLOPE FACTOR

In the only long-term oral cancer study (an F_1 generation of inbred BD-IV rats given weekly doses of 50 mg/kg chloroprene by gavage), no significant neoplastic effects were reported (Ponomarkov and Tomatis, 1980). The number of tumor-bearing animals was similar to controls. Therefore, no oral slope factor was derived for chloroprene.

II.B.1.2. DRINKING WATER UNIT RISK

N/A

II.B.1.3. EXTRAPOLATION METHOD

N/A

II.B.2. DOSE-RESPONSE DATA

N/A

II.B.3. ADDITIONAL COMMENTS

N/A

II.B.4. DISCUSSION OF CONFIDENCE

N/A

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

II.C.1.1. INHALATION UNIT RISK

Given the multiplicity of tumor sites observed in female mice exposed to chloroprene for 2 years (NTP, 1998), the derivation of the inhalation unit risk of 3.0×10^{-4} per $\mu g/m^3$ is based on the incidence of tumors in multiple organ systems: alveolar/bronchiolar adenoma or carcinoma; hemangioma/hemangiosarcoma (all organs); mammary gland adenocarcinoma, carcinoma, or adenoacanthoma; forestomach squamous cell papilloma or carcinoma; hepatocellular adenoma or carcinoma; Harderian gland adenoma or carcinoma; skin sarcoma; and Zymbal's gland carcinoma (NTP, 1998), (NTP, 1998), (NTP, 1998), (NTP, 1998). The dose metric used in the current estimate of the human equivalent concentration (HEC) is the applied or external dose because the only PBPK model available (Himmelstein et al., 2004) was determined to be inadequate for application for calculation of internal dose metrics or interspecies dosimetry extrapolations. As there is evidence that chloroprene and/or its metabolite are distributed systemically (i.e., the observation of tumors in multiple organ systems), there is the potential that chloroprene is redistributed to the lungs. For this reason, and because of chloroprene's low water solubility, low reactivity and distribution of lesions, it is most appropriately treated as a Category 3 gas for which blood-borne delivery plays a critical role. Hence, as was done for noncancer lesions, all tumors were treated as systemic effects and, since the blood:air partition coefficient for chloroprene is greater in rats than in humans, a DAF of 1.0 was applied. (see Section 5.2.3 of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010) for additional discussion).

The initial composite unit risk of 2.7×10^{-4} per $\mu g/m^3$ is based from individual unit risks derived from $BMDL_{HEC}$ values from the individual tumor types observed in female mice. The $BMDL_{HEC}$ values are the 95% lower bound on the exposure associated with a defined extra cancer risk. The individual unit risks were calculated by dividing the risk (as a fraction) by the $BMDL_{HEC}$, and represent an upper bound, continuous lifetime exposure risk estimate. For example, for hepatocellular adenoma or carcinomas:

$BMDL_{HEC10}$, lower 95% bound on exposure at 10% extra risk: 1.58×10^3 $\mu g/m^3$
BMD_{HEC10}, central estimate of exposure at 10% extra risk: 2.73×10^3 $\mu g/m^3$

The individual unit risk for this tumor: $0.1/1.58 \times 10^3$ μg/m^3 = 6.3×10^{-5} per μg/m^3

The initial composite risk was calculated using the following steps (detailed in Section 5.4.4 and Appendix C of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010):

- It was assumed that the tumor types associated with chloroprene exposure were statistically independent - that is, that the occurrence of a hemangiosarcoma, for example, was not dependent on whether there was a forestomach tumor. This assumption cannot currently be verified and if not correct could lead to an overestimate of risk from summing across tumor sites. However, NRC (1994) argued that a general assumption of statistical independence of tumor-type occurrences within animals was not likely to introduce substantial error in assessing carcinogenic potency from rodent bioassay data.

- The models previously fitted to estimate the BMDs and BMDLs were used to extrapolate to a lower level of risk (R) where the BMDs and BMDLs were in a linear range. For these data a 1×10^{-2} risk (R = 0.01) was generally the lowest risk necessary. Although this step appears to differ from the explicit recommendation of the cancer guidelines (U.S. EPA, 2005) to estimate cancer risk from a POD "near the lower end of the observed range, without significant extrapolation to lower doses," this method is recommended in the cancer guidelines as a method for combining multiple extrapolations. A sensitivity analysis considering risks nearer the lower end of the observed ranges for each tumor type (data not shown) indicated that the composite risk was essentially the same (to 2 significant digits) whether or not the individual risks were estimated in the region of 10^{-2} risk or near the PODs.

- The central tendency estimates of unit potency (that is, risk per unit of exposure) at each BMD_{01}, estimated by $0.01/BMD_{01}$, were summed across the sites listed in Table 5-6 for male mice and similarly across the sites for female mice listed in Table 5-7 (see Appendix C, Table C-5 of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010)).

- The composite unit risk, which is a 95% upper confidence limit (UCL), was calculated by assuming a normal distribution for the individual risk estimates and deriving the variance of the risk estimate for each tumor site from its 95% UCL ($0.01/BMDL_{01}$) and MLE ($0.01/BMD_{01}$) according to the following formula:

  95% UCL = MLE + 1.645 × SD or
  $0.01/BMDL_{01} = 0.01/BMD_{01} + 1.645 \times SD$

  rearranged to:

  $SD = (0.01/BMDL_{01} - 0.01/BMD_{01})/1.645$

where 1.645 is the t-statistic corresponding to a one-sided 95% confidence interval and >120 degrees of freedom, and the standard deviation (SD) is the square root of the variance of the MLE. The variances (variance = SD^2) for each site-specific estimate were summed across tumor sites to obtain the variance of the sum of the MLEs. The 95% UCL on the sum of the individual MLEs was calculated from expression (1) using the variance of the MLE to obtain the relevant SD (SD = variance$^{1/2}$).

The resulting composite unit risk for all tumor types for female mice was 2.7×10^{-4} per $\mu g/m^3$. The recommended composite upper bound estimate on human extra cancer risk from continuous lifetime exposure to chloroprene is 3×10^{-4} per $\mu g/m^3$, rounding the composite risk for female mice above to one significant digit. This unit risk should not be used with continuous lifetime exposures greater than 600 $\mu g/m^3$ (0.6 mg/m^3), the human equivalent POD for the female lung tumors, because the observed dose-response relationships do not continue linearly above this level and the fitted dose-response models better characterize what is known about the carcinogenicity of chloroprene.

Because a mutagenic mode of action for chloroprene carcinogenicity is supported by in vivo and in vitro data and relevant to humans (see Section 4.7.3.1 in the *Toxicological Review of Chloroprene* (U.S. EPA, 2010), and in the absence of chemical-specific data to evaluate the differences in susceptibility, increased early-life susceptibility is assumed and the age-dependent adjustment factors (ADAFs) should be applied, as appropriate, along with specific exposure data in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure to Carcinogens* (U.S. EPA, 2005). The inhalation unit risk of 3×10^{-4} per $\mu g/m^3$, calculated from data for adult exposures, does not reflect presumed early-life susceptibility for this chemical. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*.

The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current default ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005). The 10-fold and threefold adjustments in slope factor are to be combined with age specific exposure estimates when estimating cancer risks from early life (< 16 years age) exposure to chloroprene.

To illustrate the use of the ADAFs established in the *Supplemental Guidance* (U.S. EPA, 2005), sample calculations are presented for a lifetime risk estimate for continuous exposure from birth with a life expectancy of 70 years. The ADAFs are first applied to obtain risk estimates for continuous exposure over the three age groups:

Risk for birth through < 2 yr = 3×10^{-4} per $\mu g/m^3 \times 10 \times 2yr/70yr = 8.6 \times 10^{-5}$ per $\mu g/m^3$
Risk for ages 2 through < 16 = 3×10^{-4} per $\mu g/m^3 \times 3 \times 14yr/70yr = 1.8 \times 10^{-4}$ per $\mu g/m^3$
Risk for ages 16 until 70 = 3×10^{-4} per $\mu g/m^3 \times 1 \times 54yr/70yr = 2.3 \times 10^{-4}$ per $\mu g/m^3$

To calculate the lifetime risk estimate for continuous exposure from birth for a population with default life expectancy of 70 years, the risk associated with each of the three relevant time periods is summed:

Risk = $8.6 \times 10^{-5} + 1.8 \times 10^{-4} + 2.3 \times 10^{-4} = 5.0 \times 10^{-4}$ per $\mu g/m^3$

II.C.1.2. AIR CONCENTRATIONS AT SPECIFIED RISK LEVELS

Air concentrations at specified risk levels are not provided for chloroprene. Since chloroprene is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the unit risk and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.C.1.3. EXTRAPOLATION METHOD

Time-to-tumor Modeling. For the estimation of unit risk values, the multistage Weibull model was used with linear extrapolation from the POD(BMDLHEC) associated with a defined extra cancer risk (e.g., 10%, 5%, or 1%). The multistage Weibull model incorporates the time at which death-with-tumor occurred. The multistage Weibull model has the following form:

$$P(d) = 1 - \exp[-(b_0 + b_1 d + b_2 d^2 + \ldots + b_k d^k) \times (t - t_0)^c]$$

where P(d) represents the lifetime risk (probability) of cancer at dose d (i.e., human equivalent exposure in this case); parameters $b_i \geq 0$, for i = 0, 1, ..., k; t is the time at which the animal's tumor status, either no tumor, tumor, or unknown (e.g., missing or autolyzed) was observed; and c is a parameter estimated in fitting the model, which characterizes the change in response with age. The parameter t0 represents the time between when a potentially fatal tumor becomes observable and when it causes death and is generally set to 0 because of a lack of data to estimate the time reliably, such as interim sacrifice data. Parameters were estimated using the method of maximum likelihood estimation (MLE).

II.C.2. Dose-Response Data

Tumor type – multiple (see above)
Test species – female B6C3F$_1$ mice
Route – Inhalation
References – NTP (1998)

Tumor incidence in female B6C3F$_1$ mice exposed to chloroprene via inhalation

Tissue		Chloroprene concentration (ppm)			
		Control	12.8	32	80
All organs: hemangioma or hemangiosarcoma	Unadjusted rate First incidence (days)	4/50 541	6/49 482	18/50 216	8/50 523
Lung: alveolar/bronchiolar adenoma or carcinoma	Unadjusted rate First incidence (days)	4/50 706	28/49 447	34/50 346	42/50 324
Liver: hepatocellular adenoma or carcinoma	Unadjusted rate First incidence (days)	20/50 493	26/49 440	20/50 503	30/50 384
Skin: sarcoma	Unadjusted rate First incidence (days)	0/50 -	11/49 285	11/50 524	18/50 462
Mammary gland: carcinoma or adenoacanthoma	Unadjusted rate First incidence (days)	3/50 527	6/49 440	11/50 394	14/50 336
Forestomach: squamous cell papilloma or carcinoma	Unadjusted rate First incidence (days)	1/50 734	0/49 -	0/50 -	4/50 576
Harderian gland[a]: adenoma or carcinoma	Unadjusted rate First incidence (days)	2/50 527	5/50 621	3/50 524	9/50 467
Zymbal's gland[a]: carcinoma	Unadjusted rate First incidence (days)	0/50 -	0/50 -	0/50 -	3/50 565

[a] Harderian gland and Zymbal's gland were examined histopathologically only if a lesion was observed grossly at necropsy

Source: NTP (1998).

Dose-response modeling summary for female mouse tumors associated with inhalation exposure to chloroprene

Tumor type*	Power Parameter c[a]	BMR	Point of departure[b]				Unit risk[d] /(µg/m^3)	Composite unit risk[e,f] /(µg/m^3)
			Modeled from bioassay (ppm)		Continuous, Human equivalent[c] (µg/m^3)			
			MDL	MD	BMDL	BMD		
Lung: alveolar/ bronchiolar adenoma or carcinoma	3.8	0.1	0.88	1.20	5.69×10^2	7.71×10^2	1.8×10^{-4}	
All organs: hemangio-sarcomas, hemangiomas[f, g]	5.9	0.1	5.75	10.1	3.71×10^3	6.52×10^3	2.7×10^{-5}	
All organs: hemangio-sarcomas, hemangiomas[f, h]	1.0	0.1	11.1	14.9	7.13×10^3	9.62×10^3	1.4×10^{-5}	
Mammary gland: carcinoma or adenoacanthoma	1.0	0.1	14.1	20.4	9.06×10^3	1.32×10^4	1.1×10^{-5}	
Forestomach: squamous cell papilloma or carcinoma	4.1	0.1	46.3	67.8	2.98×10^4	4.37×10^4	3.4×10^{-6}	2.7×10^{-4}
Liver: hepatocellular adenoma or carcinoma	4.2	0.1	2.45	4.24	1.58×10^3	2.73×10^3	6.3×10^{-5}	
Harderian gland: adenoma or carcinoma	2.9	0.1	12.6	27.1	8.13×10^3	1.75×10^4	1.2×10^{-5}	
Skin: sarcoma	1.6	0.1	7.18	9.49	4.63×10^3	6.11×10^3	2.2×10^{-5}	
Zymbal's gland: carcinoma	1.1	0.05	22.5	80.5	1.45×10^4	5.19×10^4	3.5×10^{-6}	

Dose-response modeling summary for female mouse tumors associated with inhalation exposure to chloroprene

[a]Multistage-Weibull model: $P(d) = 1 - \exp[-(b_0 + b_1 d + b_2 d^2 + ... + b_k d^k) \times (t-t_0)^c]$, coefficients estimated in terms of ppm as administered in bioassay; lower stage b_i not listed were estimated to be zero. See Appendix C for modeling details.
[b]BMD = Concentration at specified extra risk; BMDL = 95% lower bound on concentration at specified extra risk.
[c]Continuous equivalent estimated by multiplying exposures by (6 hours)/(24 hours) × (5 days)/(7 days).
[d]Unit risk estimated by dividing the BMR by the BMDL.
[e]Overall unit risk estimate, across all sites listed; see text for method.
[f]Highest exposure group dropped in order to better characterize low-dose responses.
[g]Treatment of early deaths (prior to final sacrifice) with hemangiosarcomas as fatal, with all other hemangiomas and hemangiosarcomas as incidental to death.
[h]All hemangiosarcomas (and hemangiomas) were considered incidental.
* Tumor incidence data from NTP (1998).

II.C.3. ADDITIONAL COMMENTS

Supplementary information not required.

II.C.4. DISCUSSION OF CONFIDENCE

Human population variability. The extent of inter-individual variability in chloroprene metabolism has not been characterized. A separate issue is that the human variability in response to chloroprene is also poorly understood. The effect of metabolic variation, including potential implications for differential toxicity, has not been well studied. Although a mutagenic MOA indicates increased early-life susceptibility, there are no data exploring whether there is differential sensitivity to chloroprene carcinogenicity across human life stages. This lack of understanding about potential differences in metabolism and susceptibility across exposed human populations thus represents a source of uncertainty.

Choice of low-dose extrapolation approach. The MOA is a key consideration in clarifying how risks should be estimated for low-dose exposure. A multistage Weibull time-to-tumor model was the preferred model because it can account for differences in mortality and other competing risks between the exposure groups in the mouse bioassay; however, it is unknown how well this model predicts low-dose extrapolated risks for chloroprene. Cause of death information was not available for this model; if available, risk estimates would tend to be slightly higher. For example, treatment of early deaths (prior to final sacrifice) with hemangiosarcomas as fatal, with all other hemangiomas and hemangiosarcomas as incidental

to death, led to unit risks up to twofold higher than unit risks treating all hemangiosarcomas (and hemangiomas) as incidental.

Dose metric. Chloroprene is metabolized to intermediates with carcinogenic potential, most likely an epoxide. However, data sufficient to estimate quantities were not available. Under the assumption that the carcinogenic form(s) of chloroprene are produced in proportion to low-exposures of chloroprene, the derived unit risk is an unbiased estimate.

Choice of bioassay/species/gender. The NTP inhalation bioassay followed an accepted protocol, was well conducted, and extensively peer reviewed. The carcinogenic response occurs in both species and sexes of rodents (as well as in humans, as observed in occupational epidemiologic cohorts). The calculated combined unit risk is based on the most sensitive endpoint (risk of any tumor type) in the most sensitive species and gender (female mouse). There is no information on chloroprene to indicate that the observed rodent tumors are not relevant to humans. Further, no data exist to guide quantitative adjustment for differences in sensitivity among rodents and humans. While site concordance generally is not assumed across species, e.g., due to potential differences in pharmacokinetics, DNA repair, other protective systems across species and tissues (U.S. EPA, 2005), it is notable that human-mouse site concordance was observed for liver tumors. In addition, rat and mouse tumor types overlapped but included different tumor types observed for each species/sex combination. Human data were insufficient to rule out the occurrence of these additional tumor types in humans.

Cross-species scaling. Another source of uncertainty comes from the interspecies extrapolation of risk from mouse to human. The two rodent species for which bioassay data were available— mouse and rat—vary in their carcinogenic responses to chloroprene, in terms of both site specificity and magnitude of response (see Section 4). Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose (Section 3). Existing pharmacokinetic models cannot yet adequately explain the species differences in carcinogenic response, and it is possible that there are pharmacodynamic as well as pharmacokinetic differences between the mouse and rat with respect to their sensitivities to chloroprene.

While concordance of specific sites between rodents and humans (e.g., liver tumors) tends to support the relevance of rodent species to humans, lack of specific site concordance (other tumors) does not diminish concern for human carcinogenic potential. The mouse was the more sensitive species to the carcinogenic effects of chloroprene exposure. Although the derivation took into account some known differences between mice and humans in tissue

dosimetry (U.S. EPA, 1994) differences in anatomy of the upper respiratory tract and resulting differences in absorption or in local respiratory system effects are sources of uncertainty.

Statistical uncertainty at the Point of Departure (POD). Parameter uncertainty within the chosen model reflects the limited sample size of the cancer bioassay. For the multistage-Weibull model applied to this data set, there is a reasonably small degree of uncertainty at the 10% extra risk level (the POD for linear low-dose extrapolation). Central estimates of risk differed from their upper bounds by about 1.2-fold for lung tumors and for the composite risk estimates.

HEC derivation. A source of uncertainty in the derivation of the HEC comes from whether or not chloroprene induces lung tumors due to portal-of-entry or systemic effects. Systemic distribution of chloroprene is evidenced by the induction of tumors in multiple organs and suggests that chloroprene may be redistributed back to the lungs and may primarily act as a systemically delivered carcinogen. However, the contribution of either route of delivery (i.e., inhalation versus bloodstream) to the induction of lung tumors is currently unknown. Treating lung tumors as systemic effects returns the highest combined unit risk (approximately 60% greater than if lung tumors are treated as portal-of-entry effects).

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – (U.S. EPA, 2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Chloroprene* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA REVIEW

Agency Completion Date -- 09/30/2011

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Substance Name – Chloroprene
CASRN – 126-99-8

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VII. REVISION HISTORY

Chloroprene
CASRN – 126-99-8
File First On-Line – 09/30/2010

Date	Section	Description
09/30/2010	I, II, VI, VII, VIII	RfC and cancer assessment added, RfD message added

VIII. SYNONYMS

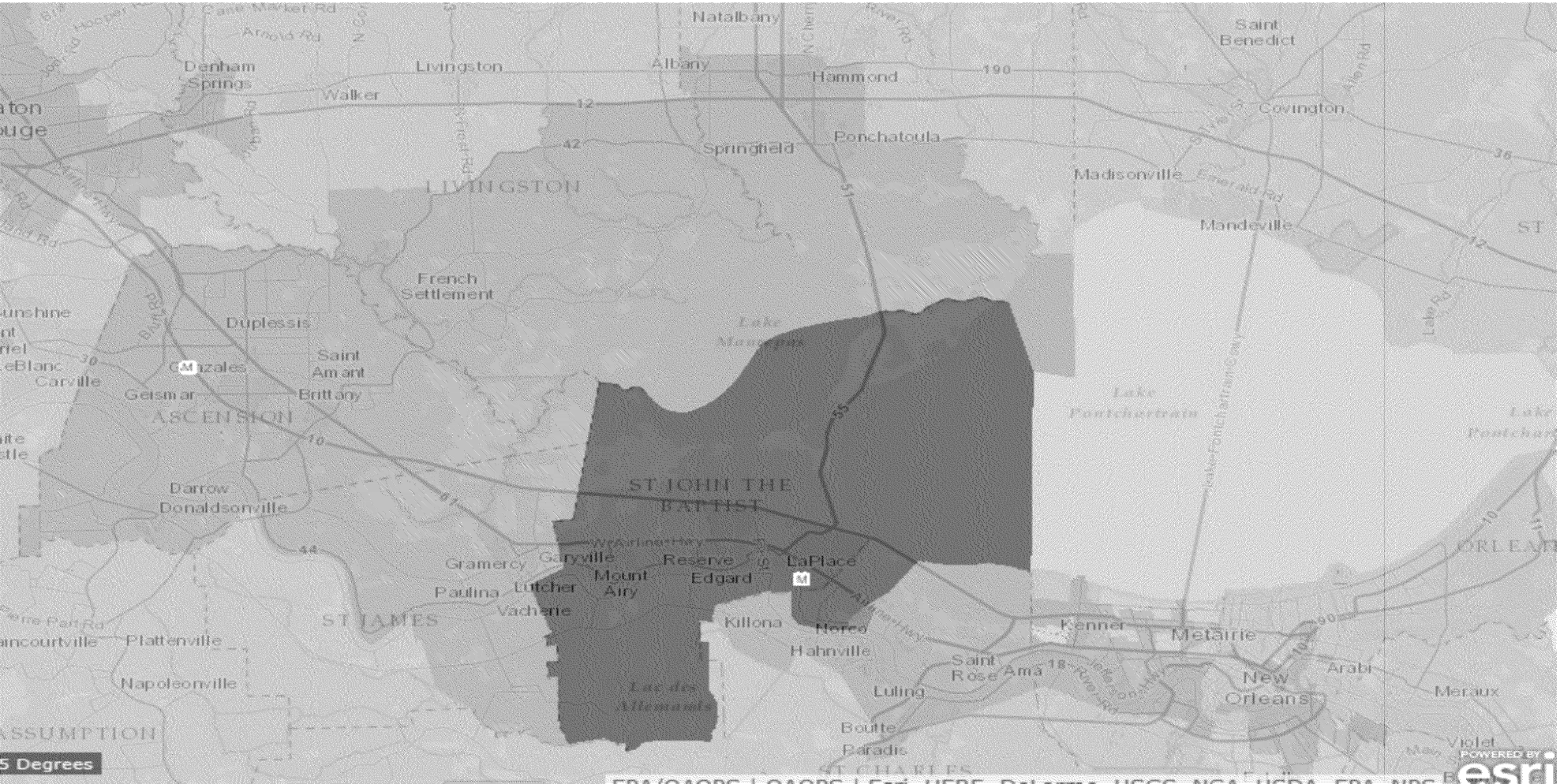
Chloroprene
CASRN – 126-99-8
Section VIII. Last Revised – 09/30/2010

- 2-chlorobuta-1,3-diene
- 2-chloro-1,3-butadiene
- chlorobutadiene

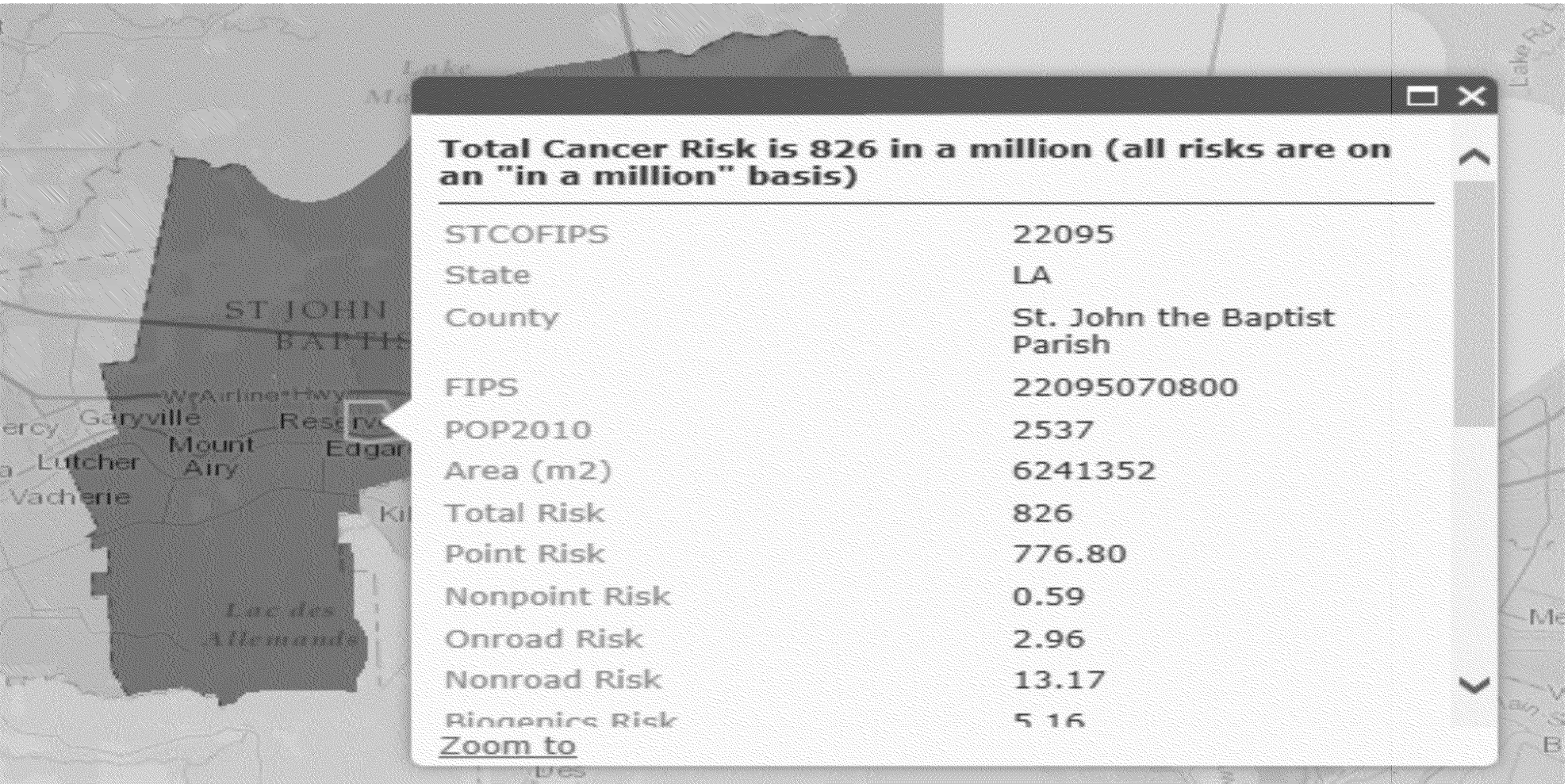
- 2-chlorobutadiene
- 2-chlorobutadiene-1,3
- beta-chloroprene

2011 NATA map – Region 6 – scale view

2011 NATA map – St John the Baptist Parish area



826 in a million *estimated* risk census tract & pop-up data



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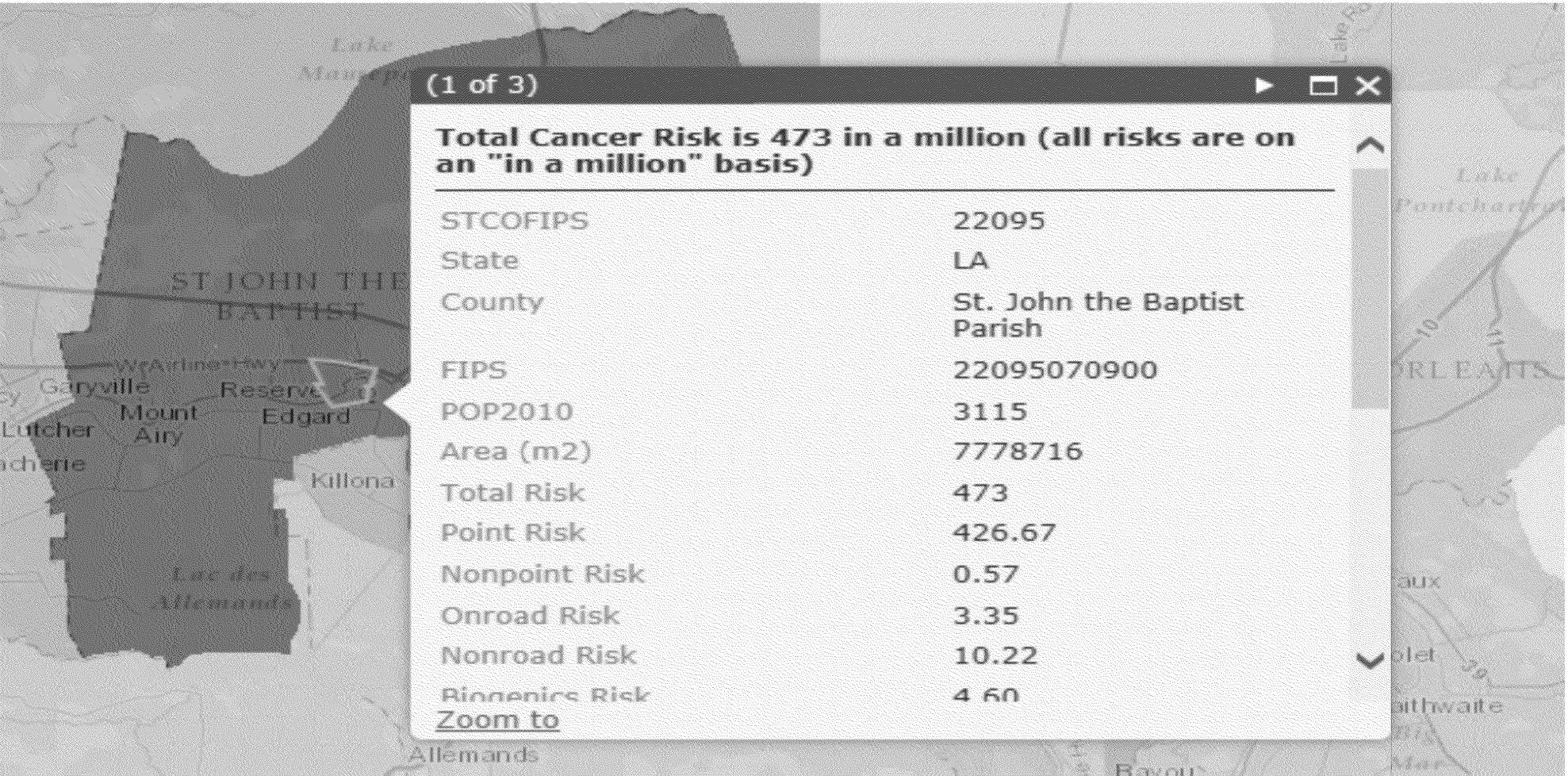

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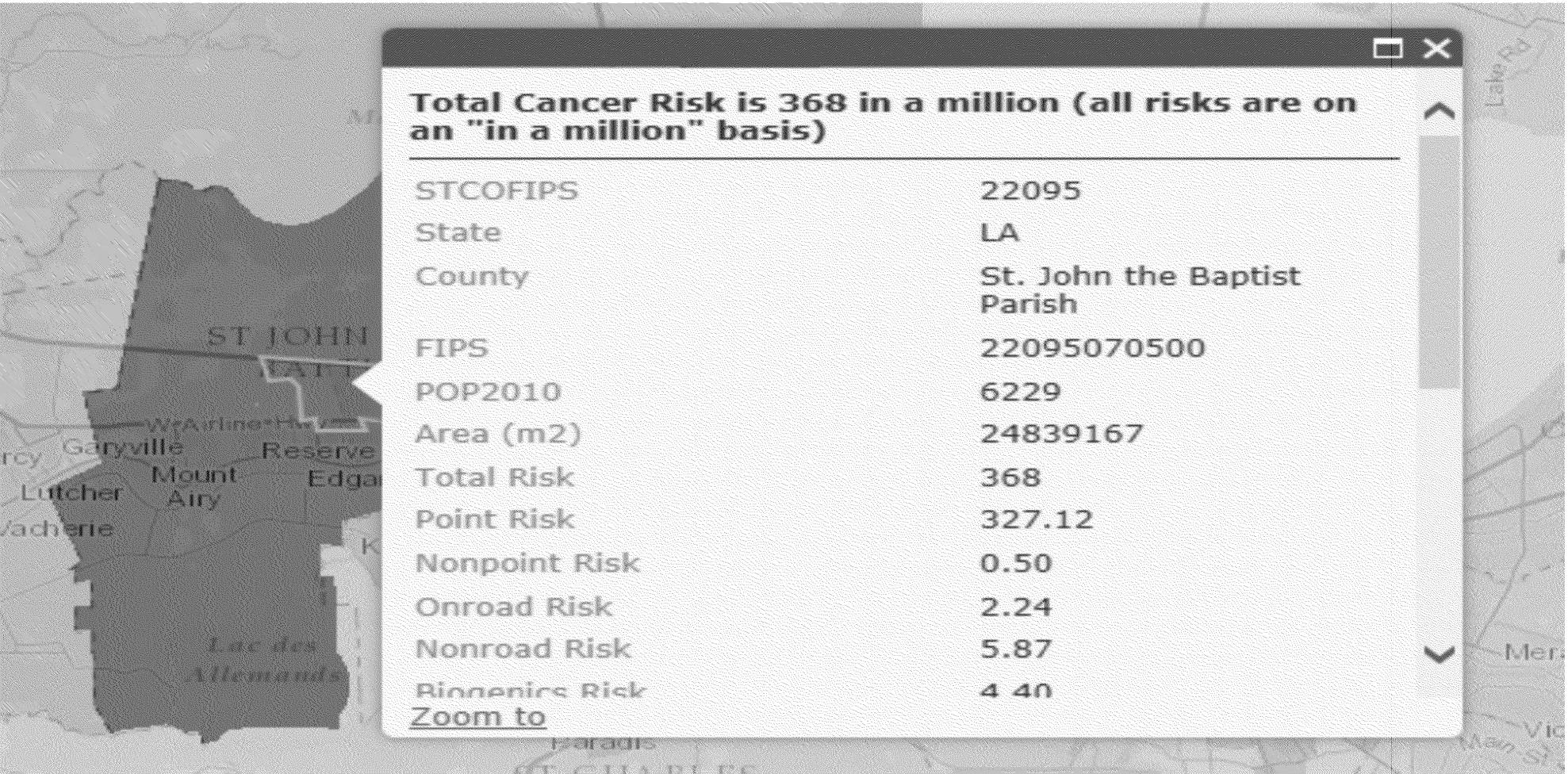

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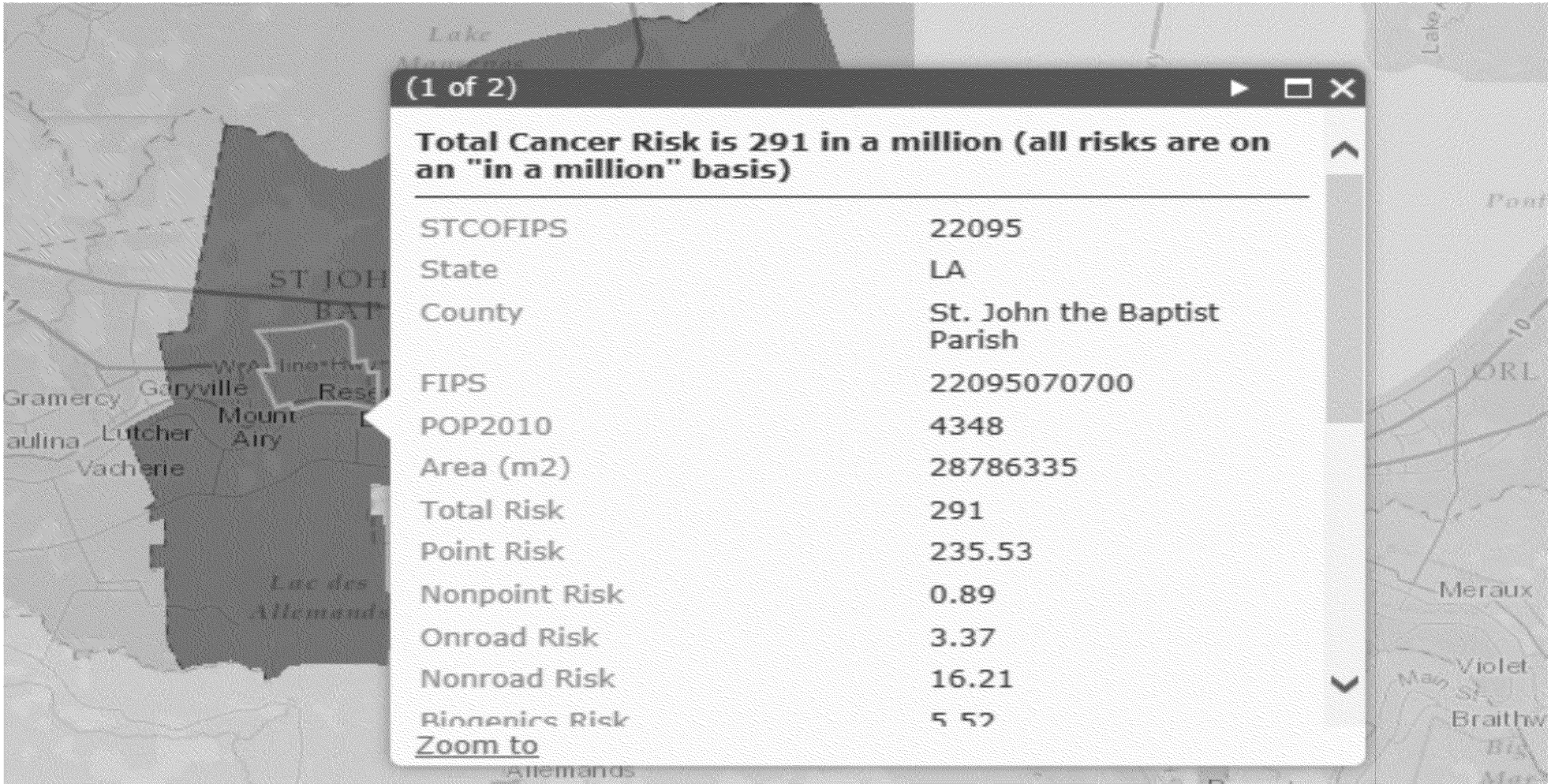
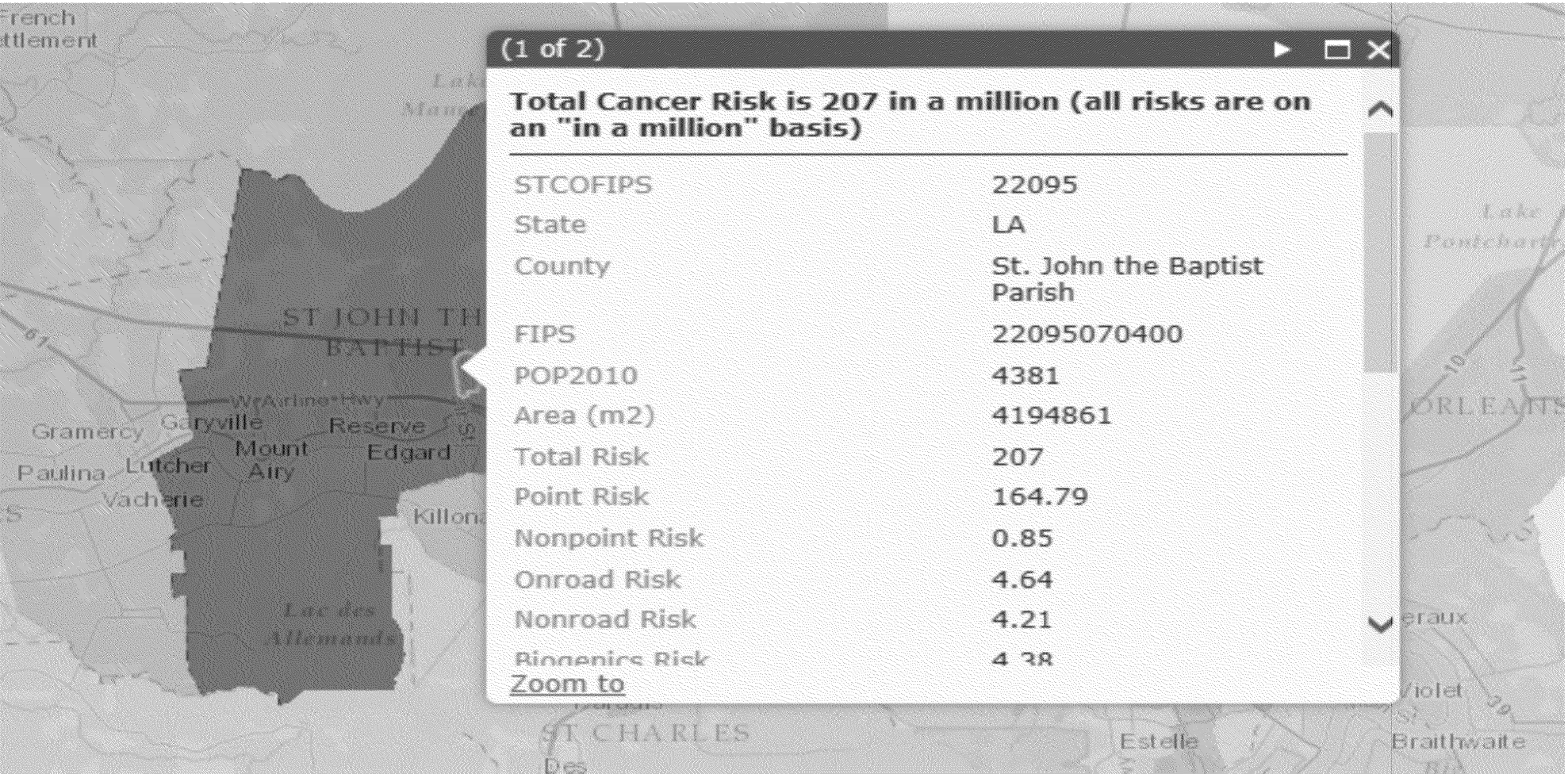
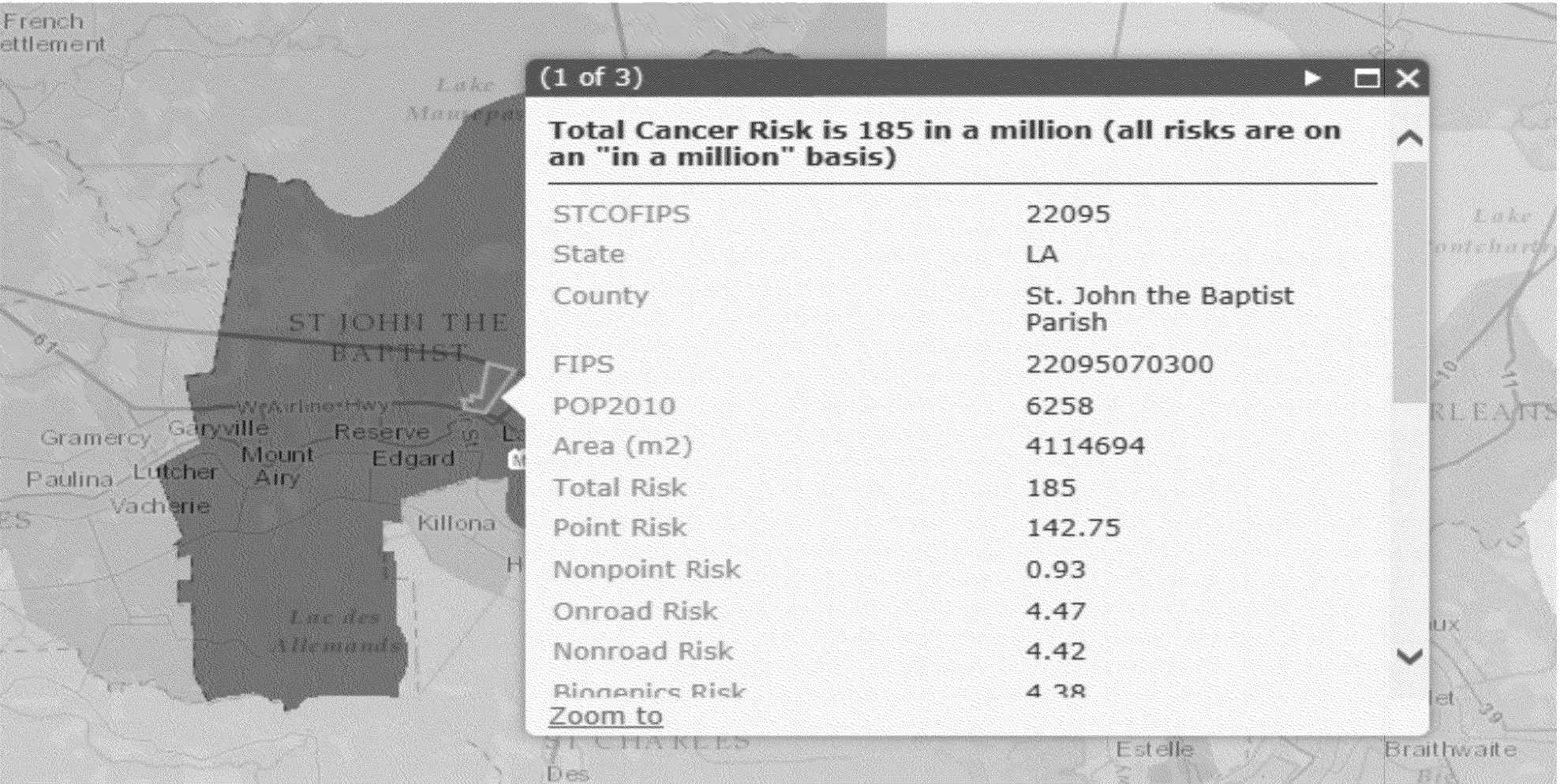


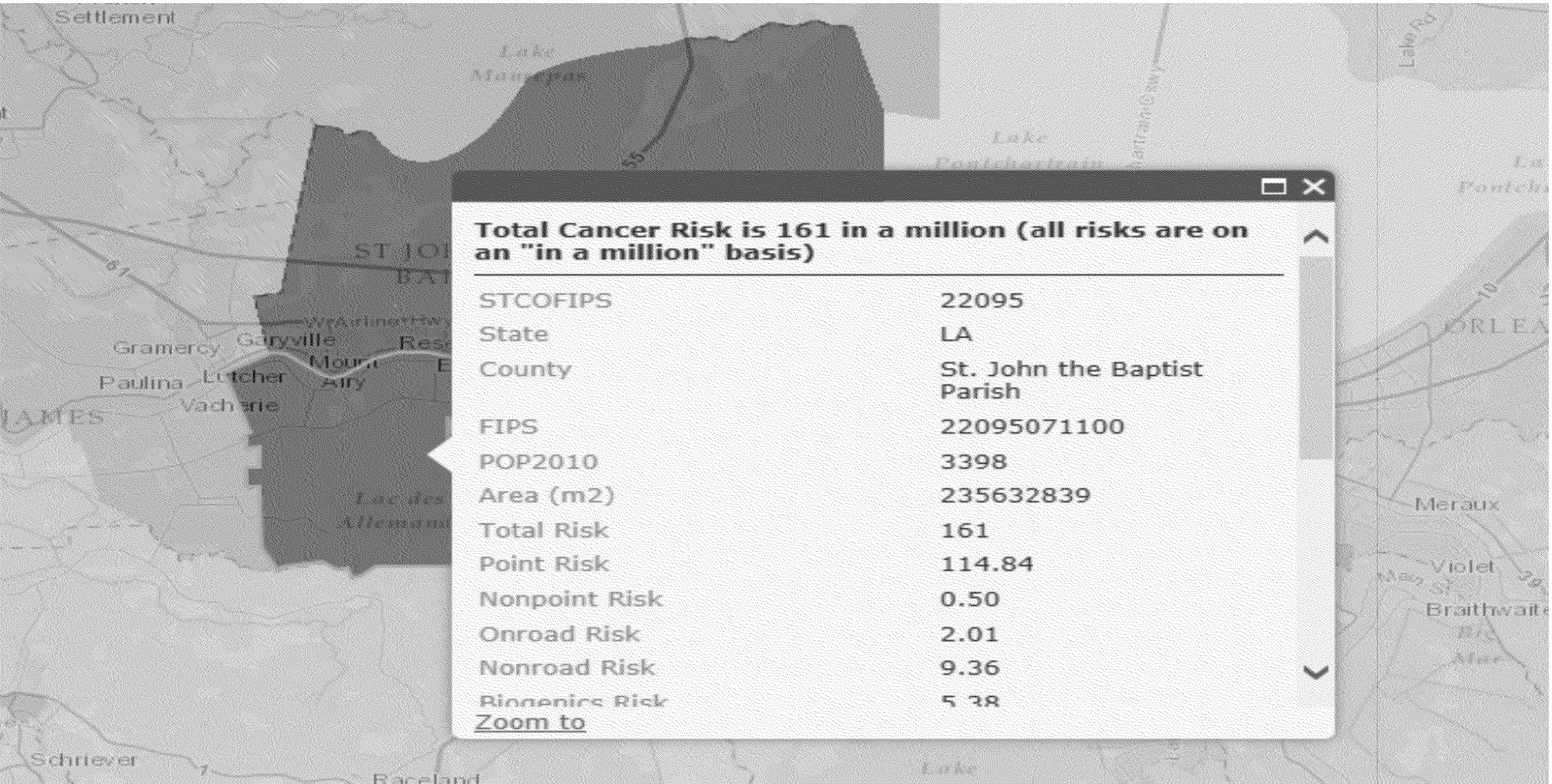
207 in a million *estimated* risk census tract & pop-up data



185 in a million *estimated* risk census tract & pop-up data



161 in a million *estimated* risk census tract & pop-up data



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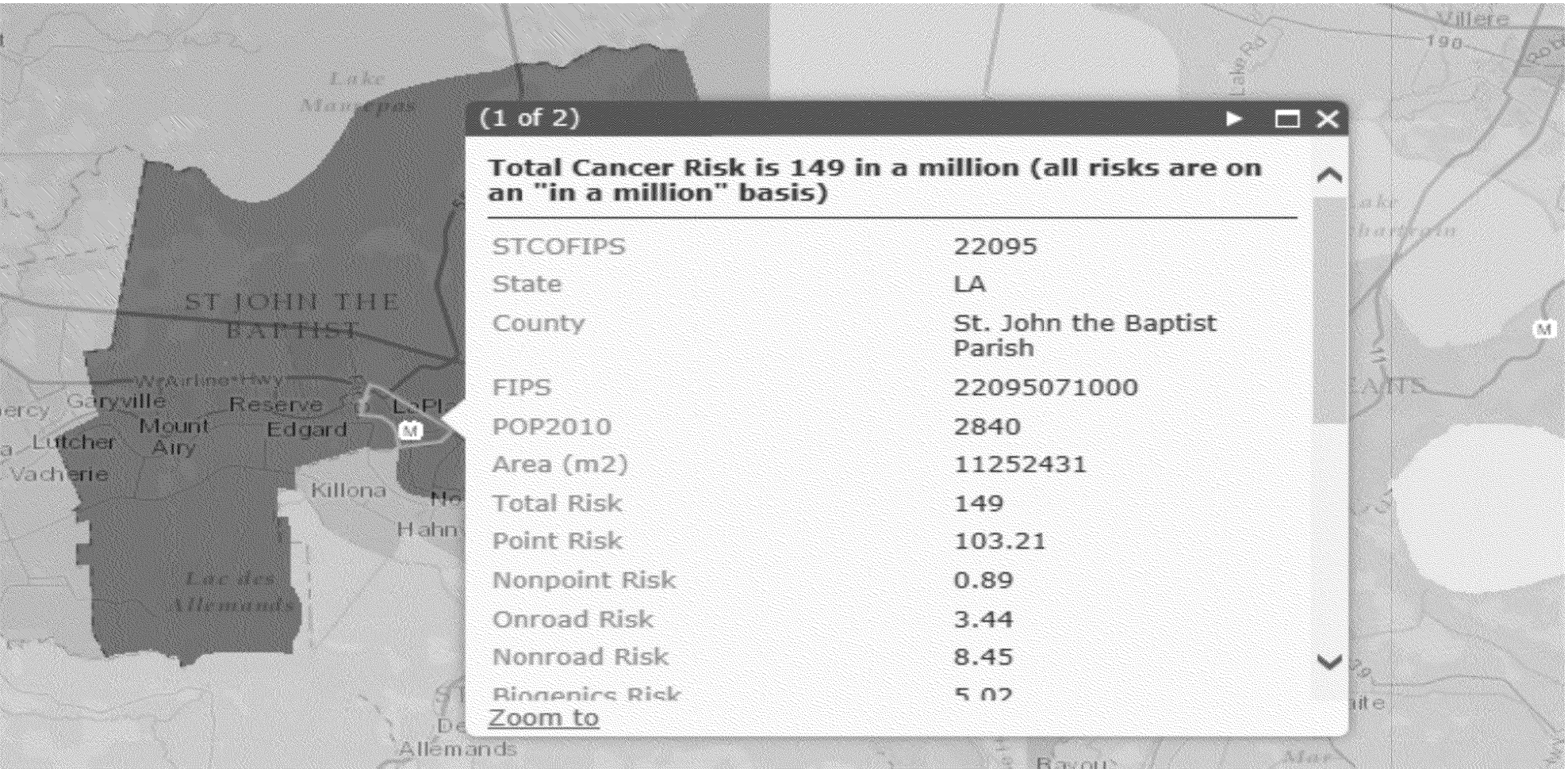

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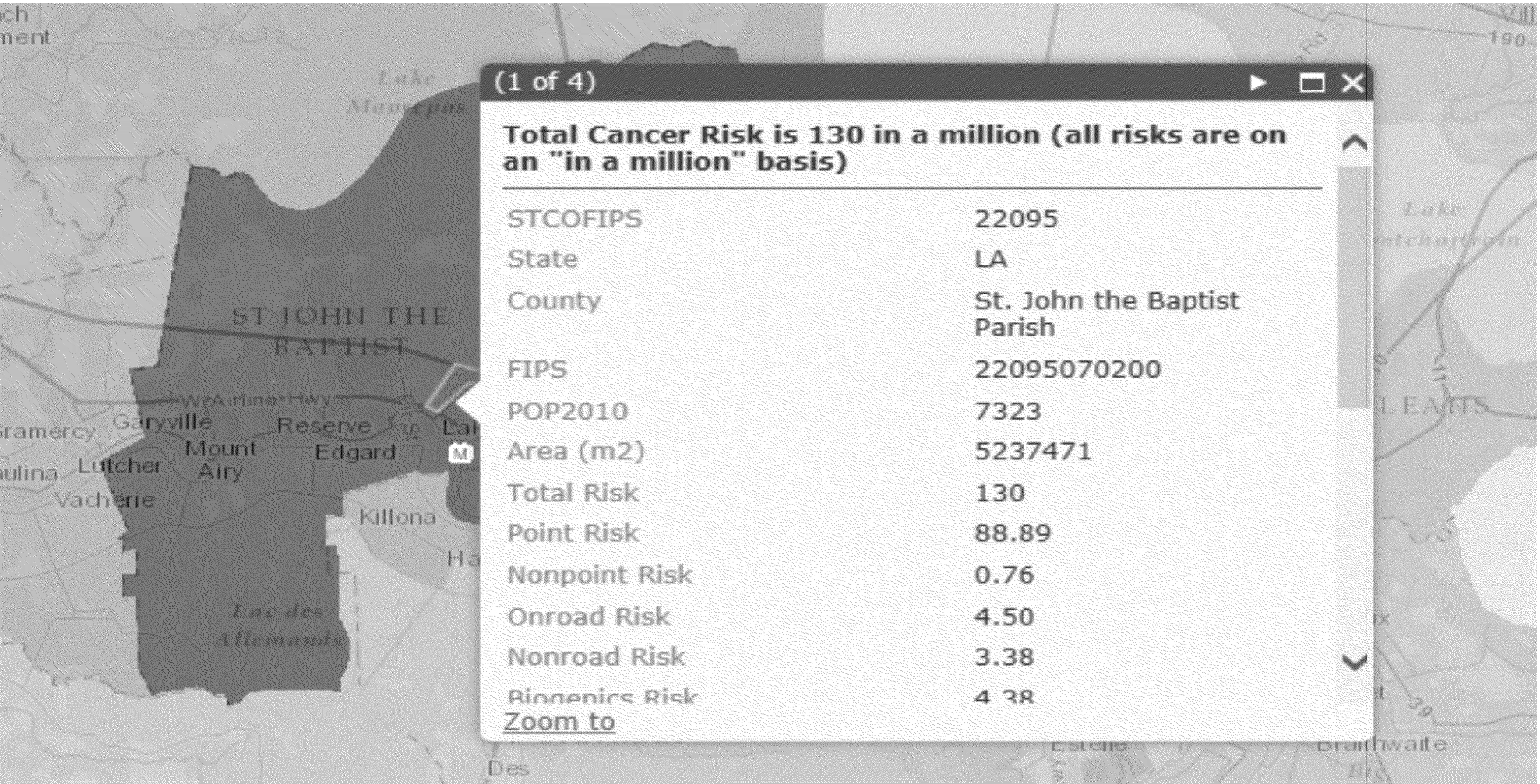
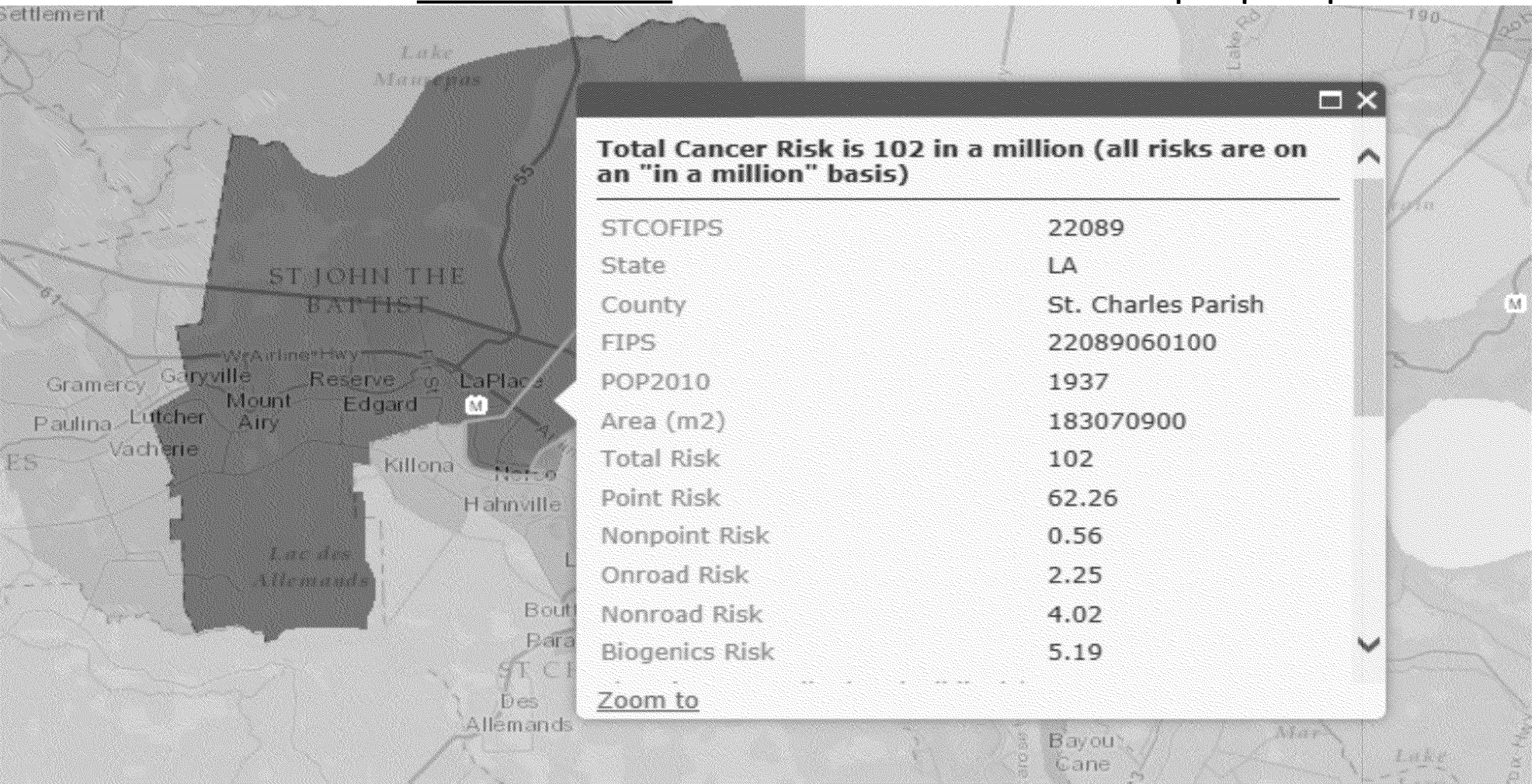
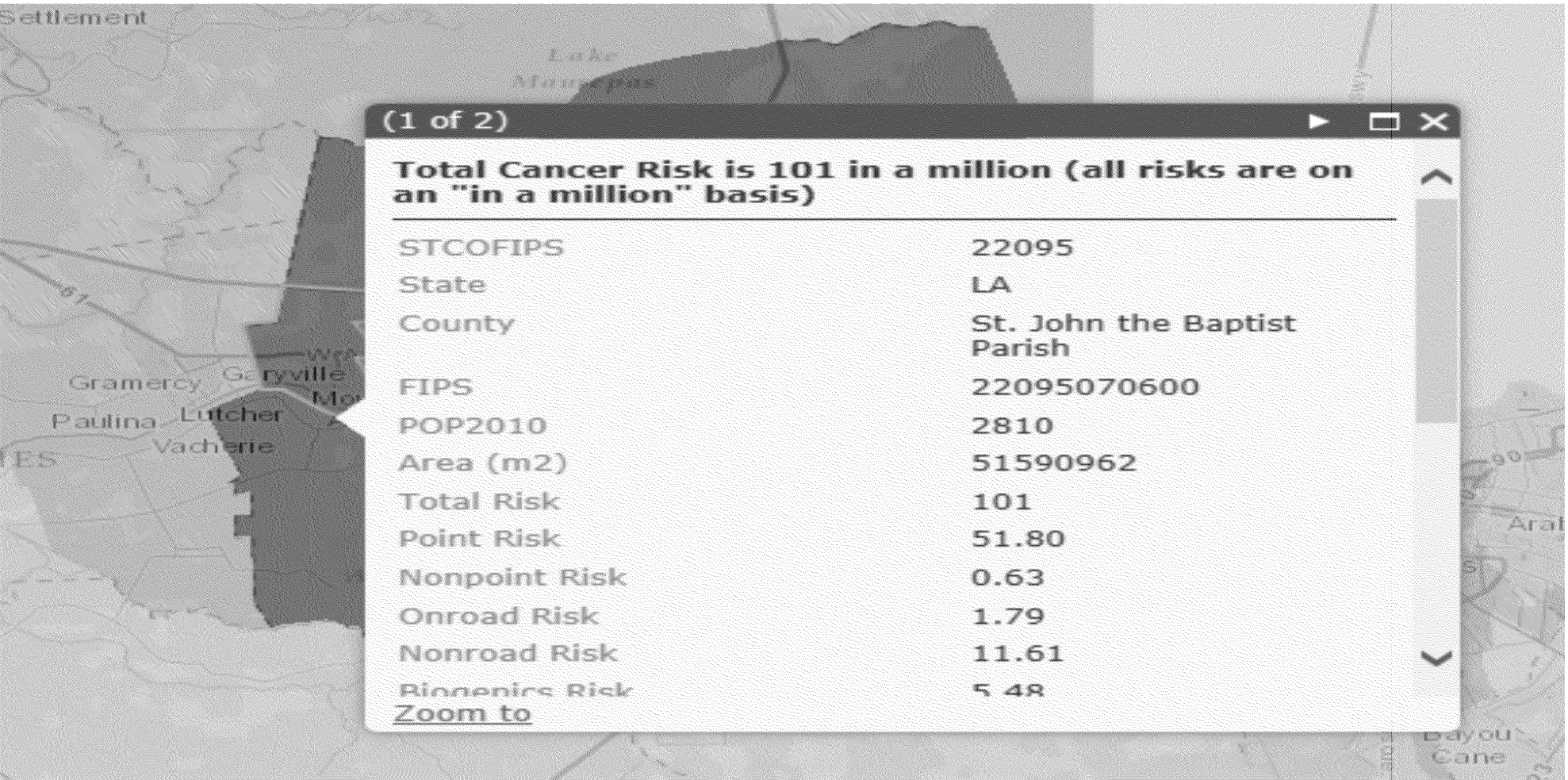


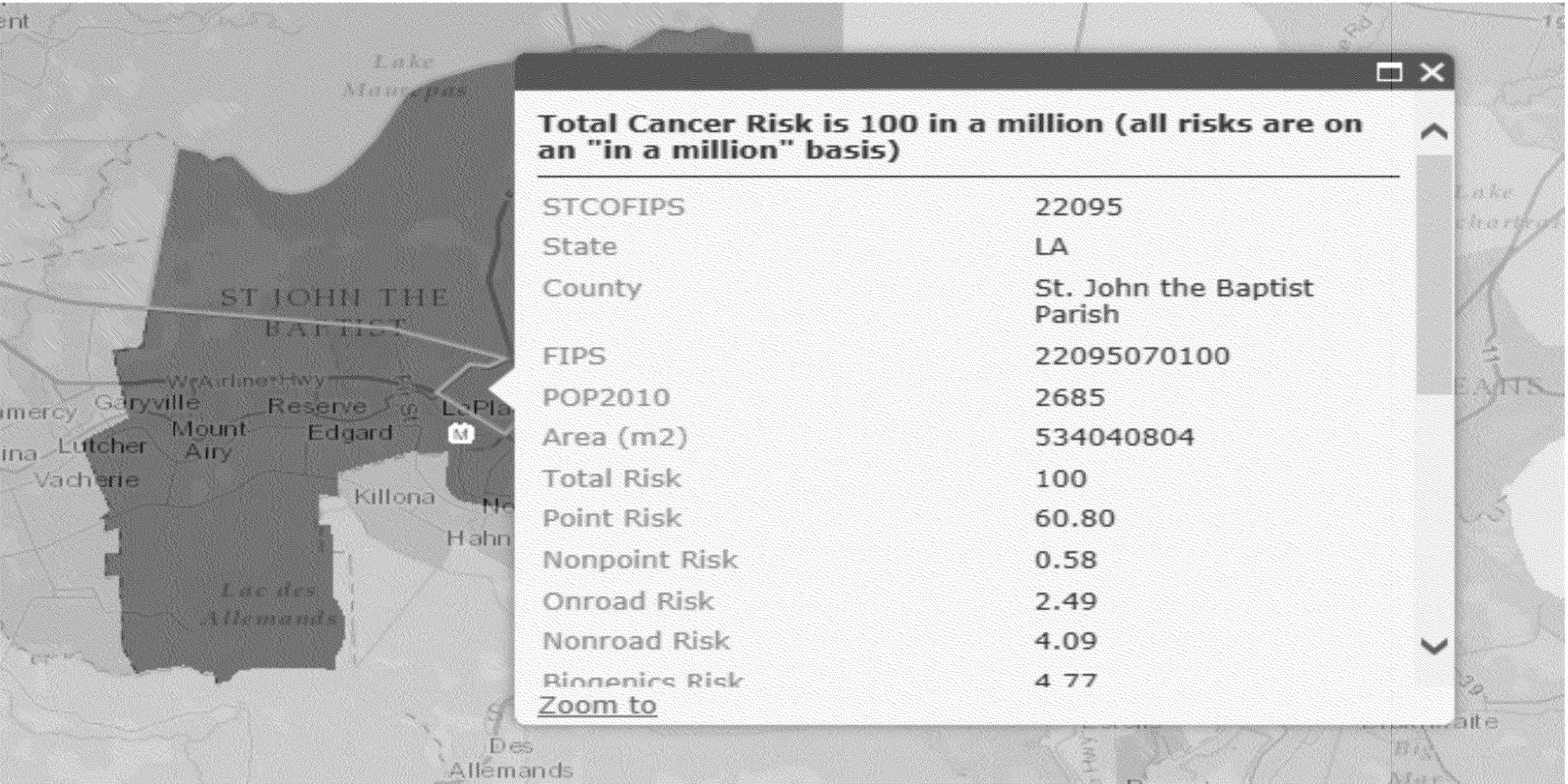
102 in a million *estimated* risk census tract & pop-up data



101 in a million *estimated* risk census tract & pop-up data



100 in a million *estimated* risk census tract & pop-up data



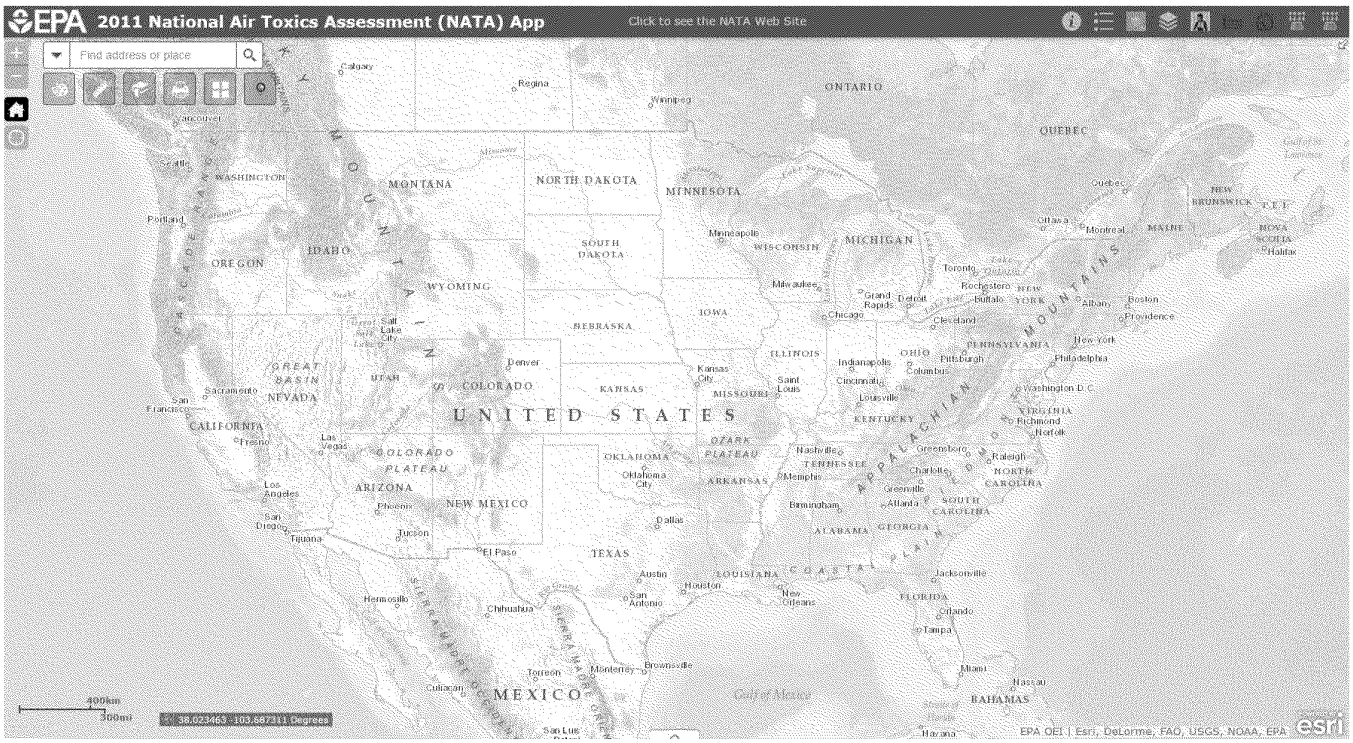
Top 25 NATA census tracts with estimated total risk > 100 in a million + 3 more in LA

	State	EPA Region	County	FIPS	Tract	Population	Point (includes railyards) Cancer Risk (per million	Total Cancer Risk (per million)	CHLOROPREN
2	LA	EPA Region 6	St. John the Baptis	22095	22095070800	2,537	776.802	826.309	768.460
3	LA	EPA Region 6	St. John the Baptis	22095	22095070900	3,115	426.667	473.139	419.106
4	LA	EPA Region 6	St. John the Baptis	22095	22095070500	6,229	327.119	367.927	320.998
5	LA	EPA Region 6	St. John the Baptis	22095	22095070700	4,348	235.541	290.549	224.896
6	LA	EPA Region 6	St. John the Baptis	22095	00000000000	45,924	209.476	253.829	201.617
7	LA	EPA Region 6	St. John the Baptis	22095	22095070400	4,381	164.790	206.649	158.515
8	PA	EPA Region 3	Allegheny	42003	42003432400	2,584	162.421	200.616	0.000
9	LA	EPA Region 6	St. John the Baptis	22095	22095070300	6,258	142.753	184.736	135.887
10	WA	EPA Region 10	King	53033	53033008200	3,280	0.507	165.898	0.001
11	LA	EPA Region 6	St. John the Baptis	22095	22095071100	3,398	114.841	160.621	107.650
12	WA	EPA Region 10	King	53033	53033008300	2,505	0.462	160.169	0.001
13	PA	EPA Region 3	Allegheny	42003	42003434000	1,781	118.956	156.302	0.000
14	WA	EPA Region 10	King	53033	53033008002	3,013	0.433	154.592	0.001
15	PA	EPA Region 3	Allegheny	42003	42003432300	2,121	117.986	152.964	0.000
16	WA	EPA Region 10	King	53033	53033008400	3,760	0.457	151.270	0.001
17	LA	EPA Region 6	St. John the Baptis	22095	22095071000	2,840	103.207	148.656	92.120
18	PA	EPA Region 3	Philadelphia	42101	42101000402	3,142	2.179	148.007	0.000
19	WA	EPA Region 10	King	53033	53033008100	4,070	0.608	144.848	0.001
20	NY	EPA Region 2	New York	36061	36061026500	7,021	0.660	143.002	0.000
21	WA	EPA Region 10	King	53033	53033008500	4,341	0.632	138.669	0.001
22	CA	EPA Region 9	San Francisco	06075	06075012502	3,821	0.352	132.130	0.000
23	IL	EPA Region 5	Cook	17031	17031803606	8,287	0.948	130.025	0.000
24	LA	EPA Region 6	St. John the Baptis	22095	22095070200	7,323	88.893	129.680	82.074
25	WA	EPA Region 10	King	53033	53033007500	6,282	0.376	129.563	0.001
26	PA	EPA Region 3	Philadelphia	42101	42101000804	3,609	2.596	128.951	0.000
111	LA	EPA Region 6	St. Charles Parish	22089	22089060100	1,937	62.256	101.898	37.537
118	LA	EPA Region 6	St. John the Baptis	22095	22095070600	2,810	51.798	100.668	41.876
121	LA	EPA Region 6	St. John the Baptis	22095	22095070100	2,685	60.796	100.426	50.524

Note: census tract “00000000000” shows parish-wide total population and parish-wide *average* estimated risks

Quick Start Guide to the 2011 National Air Toxics Assessment (NATA) App

The 2011 National Air Toxics Assessment (NATA) App is a tool to aid NATA users in visualizing the emissions data and the modeling results, including risk and ambient concentration estimates, of the 2011 NATA. The app is browser based, so there are no special software requirements. The NATA App is accessible on the web and on mobile devices.



When the app is first opened, you see a blank topographic map of the continental US. No map layers are displayed at this scale because the data in most of the layers is not meaningful at this resolution.

Navigating

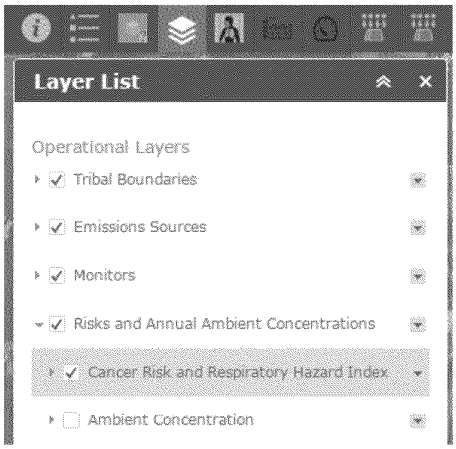
You can navigate the map in several ways. You can use the zoom in/zoom out at the top left in the app. If you zoom in far enough, layers will start to appear. To see which layers are on at any given scale, click on the Legend widget, which is one of the header widgets in the top right of the app.

There are four main layers of data in the app:

1) **Tribal Boundaries** - EPA Office of Environmental Information dataset based on US Census Bureau 2010 tribal boundary layer data for the lower 48 United States and Bureau of Land Management Alaska State Office data for tribes in Alaska.
2) **Emissions Sources** - Emissions data (in tons per year) for all sources modeled for NATA. All sources were modeled in **CMAQ**, and all sources except fires and biogenics were modeled in **AERMOD**.

3) **Monitoring Data** - Annual (2005 - 2013) statistics of measured ambient air toxics concentrations (in micrograms per cubic meter (µg/m3)) and associated risk estimates for individual monitoring sites based on the data from the **Air Monitoring Archive (AMA), Phase IX**
4) **Risks and Annual Ambient Concentrations** - Modeled annual ambient concentrations and risks at the census tract level. All concentrations have units of µg/m^3, and all cancer risk estimates are on a per million basis. For example, a cancer risk of 10 means the estimated lifetime risk of cancer is 10 in a million (that is, the estimated probability of getting cancer is 0.00001).

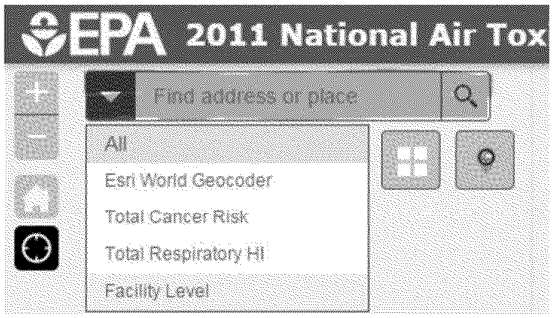
To change which layers are displayed, click on the Layer List widget, which is also in the header at the top right of the app.



You can check the boxes for the layers you want on, and uncheck those you don't want displayed. To expand the main layers, click on the layer name.

There are ways to navigate other than zooming. To go to the area you are currently in, click on the My Location widget (highlighted in yellow below). This feature is especially useful when using the app on a mobile device.

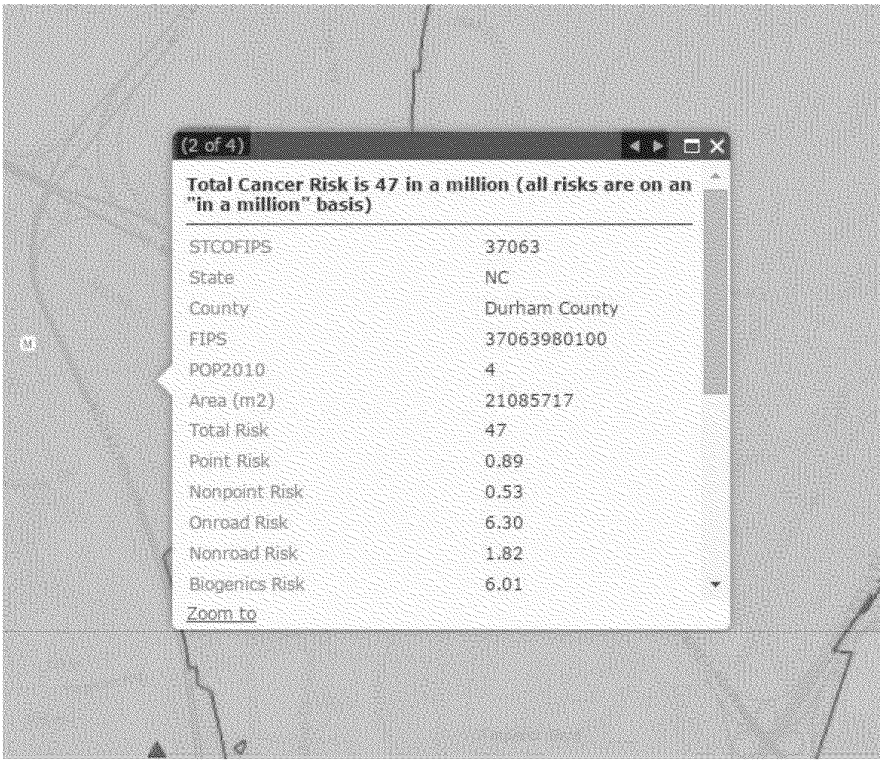
You can use the search window to search for a location by State, county, city, zipcode, or longitude and latitude coordinates (longitude first, and negative for the western hemisphere). You can also search using the layers in the map by clicking the dropdown for the search window and selecting which dataset you want to search



The Cancer Risk and Respiratory Hazard Index (HI) layers can be searched by 11-digit census tract number, and the Facility Level layer of stationary sources can be searched by all or part of a facility name, or by a facility's EPA Emission Inventory System (EIS) facility ID. Note that the facility search returns only 20 results, so if you search the name of a chain of gas stations, for example, you likely will not get all of them. The default is to search all the layers in the dropdown, which will take longer than if you specify which layer you want to search. For example, if you want to search by city name, choose the ESRI World Geocoder.

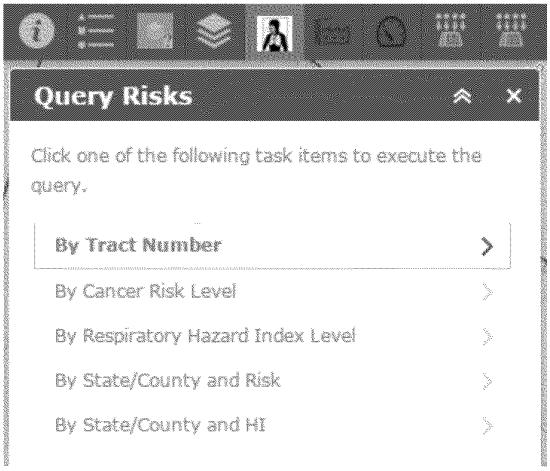
Popups

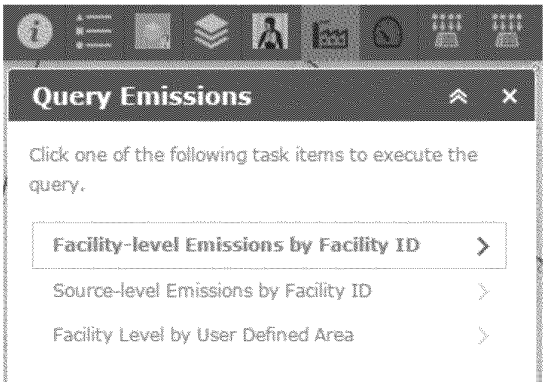
For each layer that is displayed (at the current map scale), a popup window will appear when a point in the map is clicked. A single popup window will appear, with arrows in the popup header that can be clicked to look through the popups for all layers that have features at the clicked point. The popups for the emissions layers contain tabular data about the sources clicked. The popups for the risk layers include tabular data and pie charts that show the contributions to total risk by source group and pollutant. There are no popups for monitors; those data can be accessed by running a query.

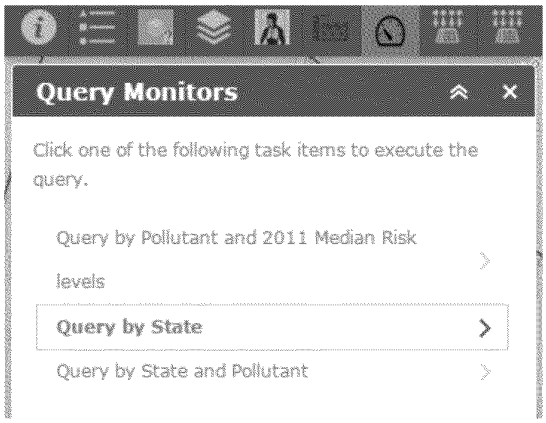


Queries

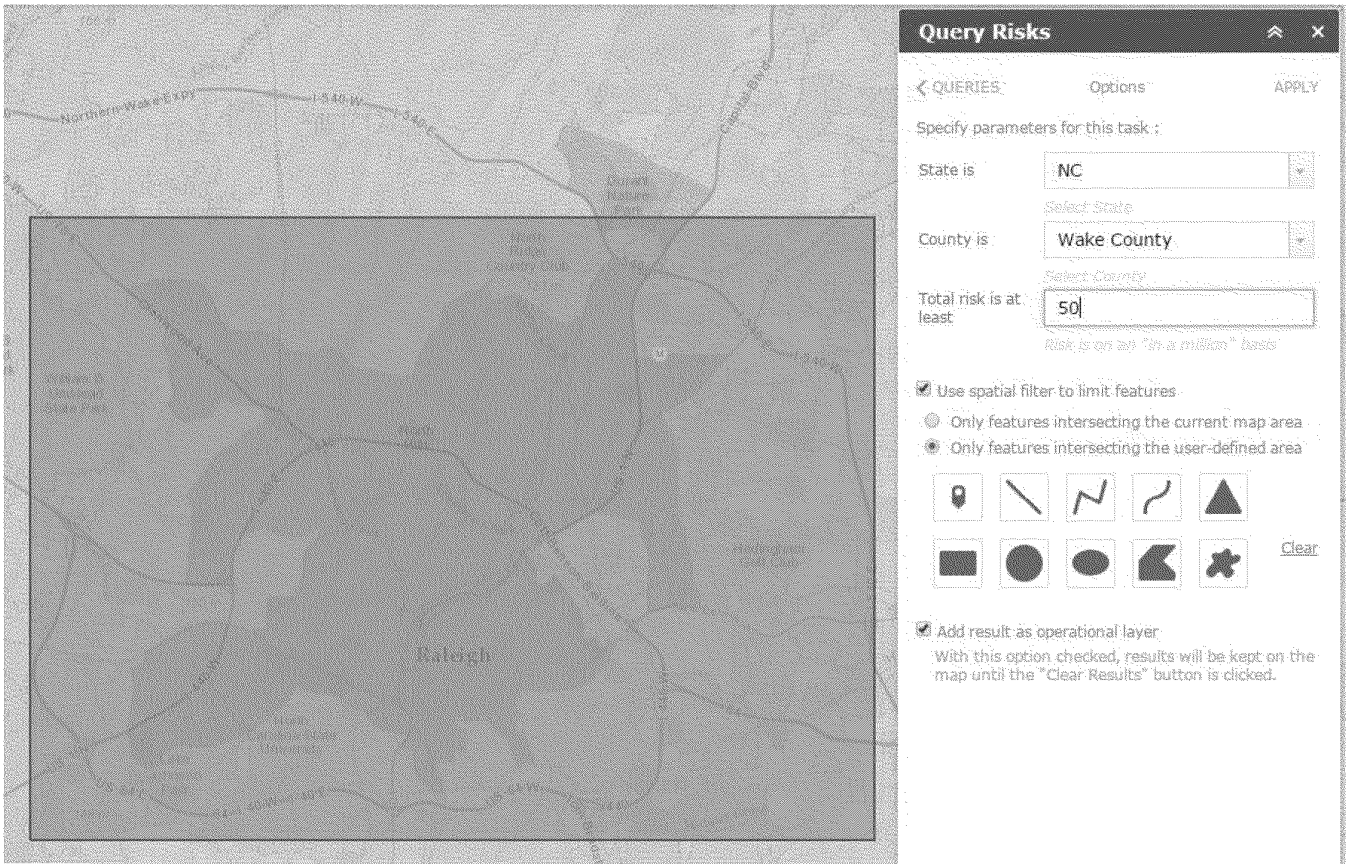
There are three main query options: risk, emissions, and monitors.



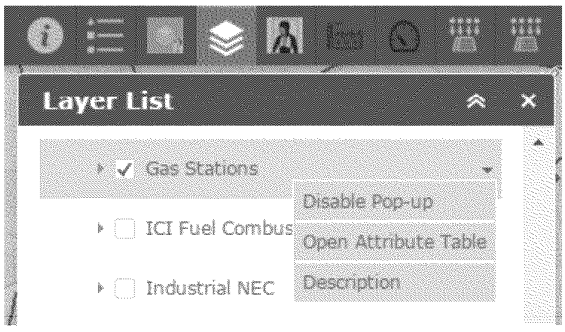




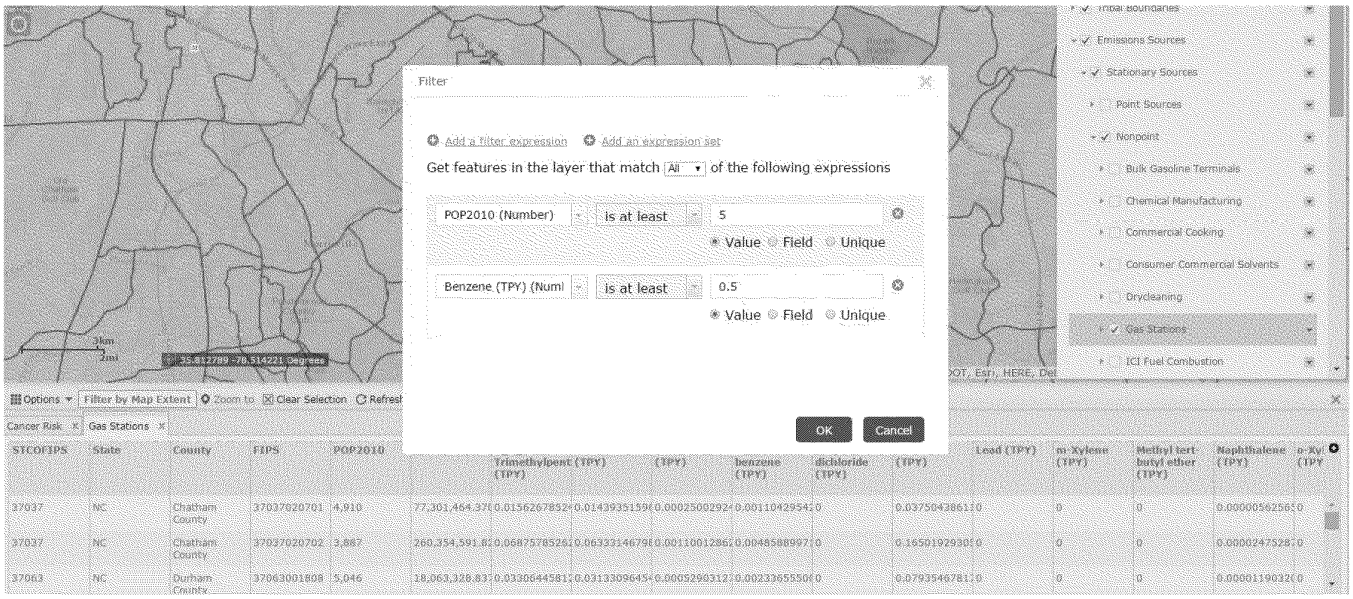
To run a query, select one of the query options, and choose the criteria by which you want to query the data. For example, below is a "By State/County and Risk" query of census tracts with total cancer risk of at least 50 in a million in Wake County, NC. A spatial filter has been used to limit the area over which the query willapply. The spatial filter can be a rectangular area as shown below or other shapes. The spatial filter can also be the current map extent (the first option under spatial filter). Finally, the box has been checked to add the query results as an operational layer in the map. This should always be checked so the results will be added to thelayer list and the attribute table of the results can be viewed.



Although there are not specific queries for all layers in the app, these layers can still be queried by opening the attribute table of the layer, and filtering the datausing criteria similar to those included in the specific queries in the app. For example, this is how to open the attribute table for the Gas Stations emissions layer:

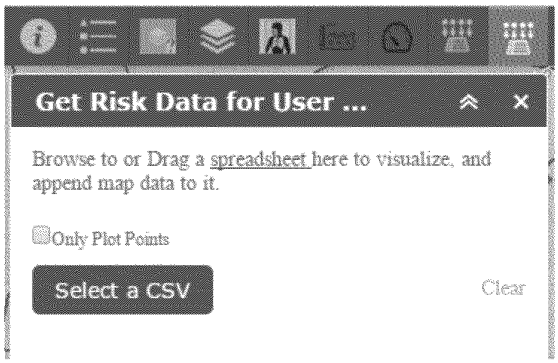


While in the attribute table, click on the "Options" dropdown and select "Filter". This is an example of a query of the Gas Stations data for census tracts with at least five people in them and with benzene emissions of at least 0.5 tons per year:



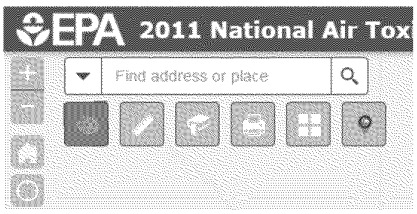
The results of the filter are not added as an operational layer as they are with the query widgets in the app, but the data can be viewed, sorted (by clicking on the field names), and downloaded (by selecting "Export All to CSV", under "Options"). Note that the maximum number of records that can be exported is 1000.

There is the option in the NATA App to input a user-supplied file of point locations and display those locations on the map. The coordinate field names that are recognized and can be plotted are lat, latitude, y, ycenter, and point_y (for latitude), and lon, long, longitude, x, xcenter, point_x (for longitude). There is also the ability to "enrich" the point locations with some of the data in the map, including risk and ambient concentration data. For example, if you wanted to plot the locations of schools and get the risk estimates for the census tracts that the schools are in, you would select your comma-separated value (CSV) file of school data by browsing for it or dragging and dropping on the widget window. The points would be plotted, and an operational layer of your results would be added to the layer list.



Other Widgets

Below is a description of other basic widgets that are available in the app.

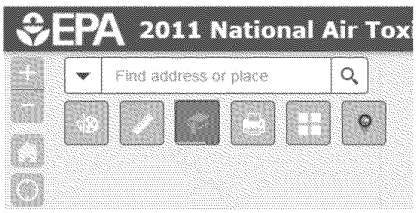


Draw Widget

The Draw widget enables users to draw basic graphics and text on the map. It provides basic sketching and redlining functionality for the web application. Note that when "Clear" is clicked, the widget removes all objects drawn and not just the most recently drawn.

Measurement Widget

The Measurement widget allows the user to measure the area of a polygon, length of a line, or find the coordinates of a point.

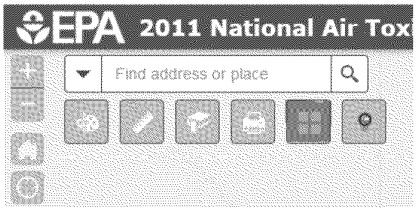


Bookmark Widget

The Bookmark widget enables users to save the map view extents of frequently viewed areas so as to easily go to those areas in the future. This could be useful for printing maps with consistent extents every time.

Print Widget

The Print widget enables users to print basic maps, which include a legend and scale bar. It is possible to create more detailed maps (e.g., including popup data and other information) by using readily available tools such as the Windows Snipping Tool.



Basemap Widget

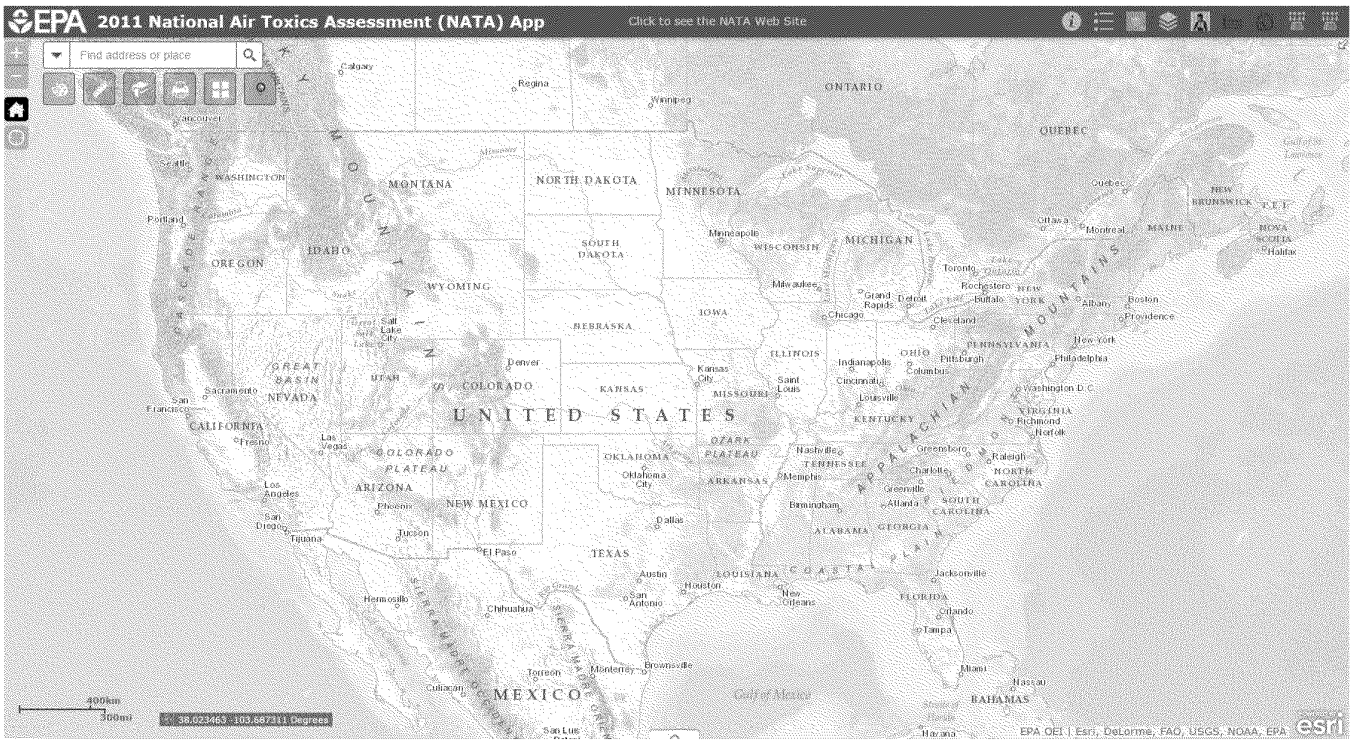
The Basemap widget allows to select which basemap will be displayed. Options include aerial imagery, street maps, and terrain maps.

Street View Imagery Widget

The Street View Imagery widget provides users with several options for viewing street-level and birds-eye imagery. Simply check the boxes for the imagery type, and click on a location in the map to see the imagery at that point

Quick Start Guide to the 2011 National Air Toxics Assessment (NATA) App

The 2011 National Air Toxics Assessment (NATA) App is a tool to aid NATA users in visualizing the emissions data and the modeling results, including risk and ambient concentration estimates, of the 2011 NATA. The app is browser based, so there are no special software requirements. The NATA App is accessible on the web and on mobile devices.



When the app is first opened, you see a blank topographic map of the continental US. No map layers are displayed at this scale because the data in most of the layers is not meaningful at this resolution.

Navigating

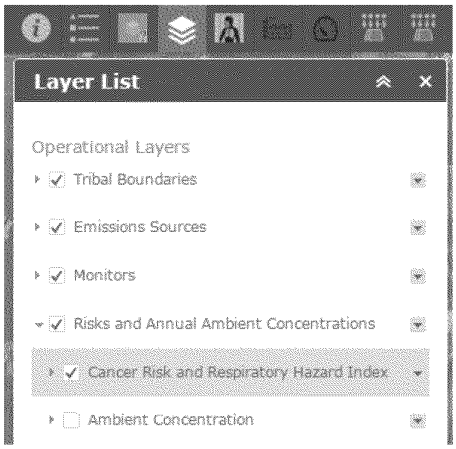
You can navigate the map in several ways. You can use the zoom in/zoom out at the top left in the app. If you zoom in far enough, layers will start to appear. To see which layers are on at any given scale, click on the Legend widget, which is one of the header widgets in the top right of the app.

There are four main layers of data in the app:

1) **Tribal Boundaries** - EPA Office of Environmental Information dataset based on US Census Bureau 2010 tribal boundary layer data for the lower 48 United States and Bureau of Land Management Alaska State Office data for tribes in Alaska.
2) **Emissions Sources** - Emissions data (in tons per year) for all sources modeled for NATA. All sources were modeled in **CMAQ**, and all sources except fires and biogenics were modeled in **AERMOD**.

3) **Monitoring Data** - Annual (2005 - 2013) statistics of measured ambient air toxics concentrations (in micrograms per cubic meter (µg/m3)) and associated risk estimates for individual monitoring sites based on the data from the **Air Monitoring Archive (AMA), Phase IX**
4) **Risks and Annual Ambient Concentrations** - Modeled annual ambient concentrations and risks at the census tract level. All concentrations have units of µg/m^3, and all cancer risk estimates are on a per million basis. For example, a cancer risk of 10 means the estimated lifetime risk of cancer is 10 in a million (that is, the estimated probability of getting cancer is 0.00001).

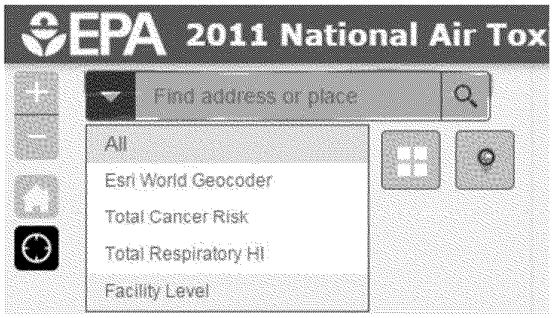
To change which layers are displayed, click on the Layer List widget, which is also in the header at the top right of the app.



You can check the boxes for the layers you want on, and uncheck those you don't want displayed. To expand the main layers, click on the layer name.

There are ways to navigate other than zooming. To go to the area you are currently in, click on the My Location widget (highlighted in yellow below). This feature is especially useful when using the app on a mobile device.

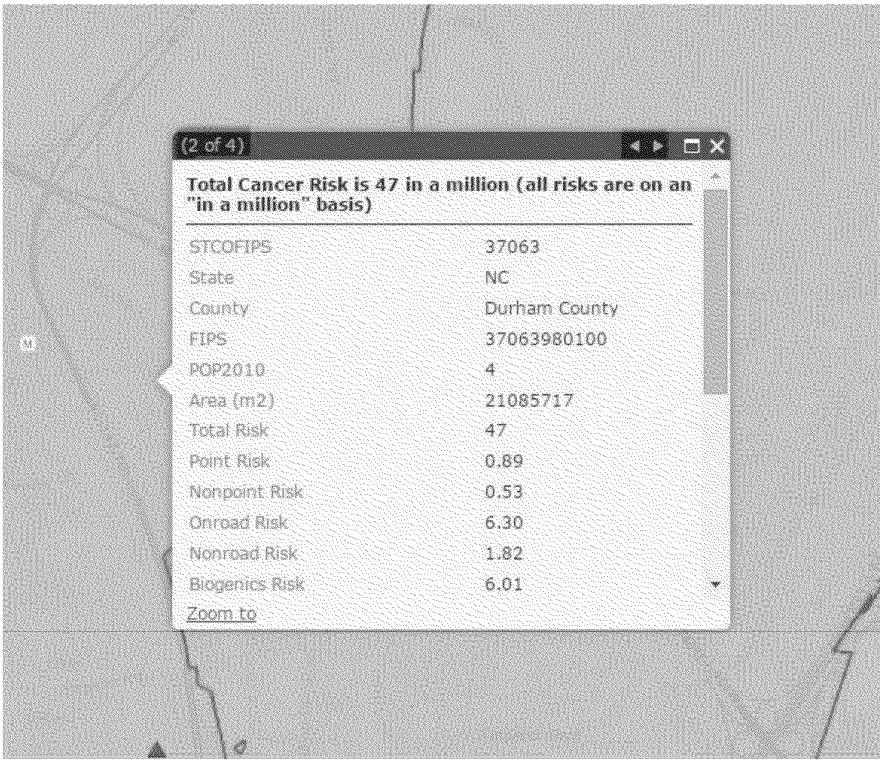
You can use the search window to search for a location by State, county, city, zipcode, or longitude and latitude coordinates (longitude first, and negative for the western hemisphere). You can also search using the layers in the map by clicking the dropdown for the search window and selecting which dataset you want to search



The Cancer Risk and Respiratory Hazard Index (HI) layers can be searched by 11-digit census tract number, and the Facility Level layer of stationary sources can be searched by all or part of a facility name, or by a facility's EPA Emission Inventory System (EIS) facility ID. Note that the facility search returns only 20 results, so if you search the name of a chain of gas stations, for example, you likely will not get all of them. The default is to search all the layers in the dropdown, which will take longer than if you specify which layer you want to search. For example, if you want to search by city name, choose the ESRI World Geocoder.

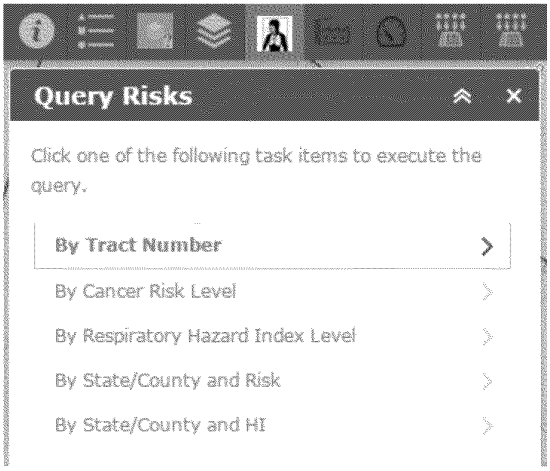
Popups

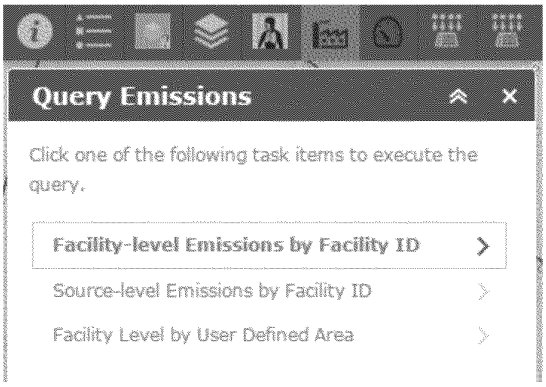
For each layer that is displayed (at the current map scale), a popup window will appear when a point in the map is clicked. A single popup window will appear, with arrows in the popup header that can be clicked to look through the popups for all layers that have features at the clicked point. The popups for the emissions layers contain tabular data about the sources clicked. The popups for the risk layers include tabular data and pie charts that show the contributions to total risk by source group and pollutant. There are no popups for monitors; those data can be accessed by running a query.

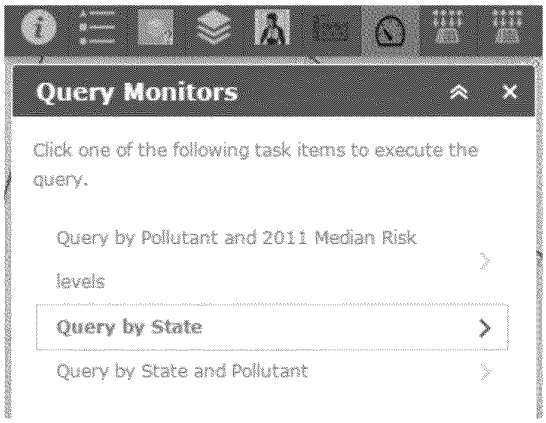


Queries

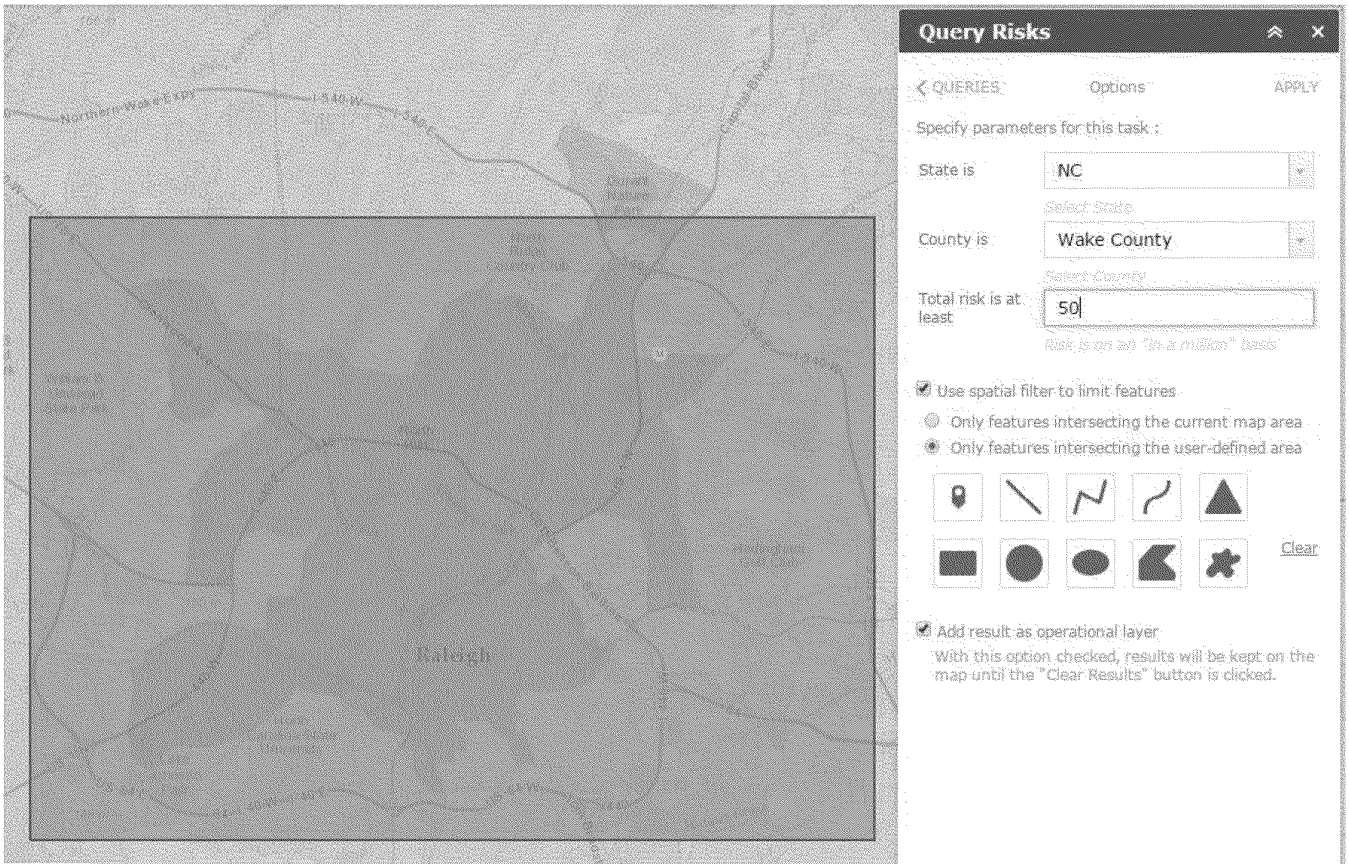
There are three main query options: risk, emissions, and monitors.



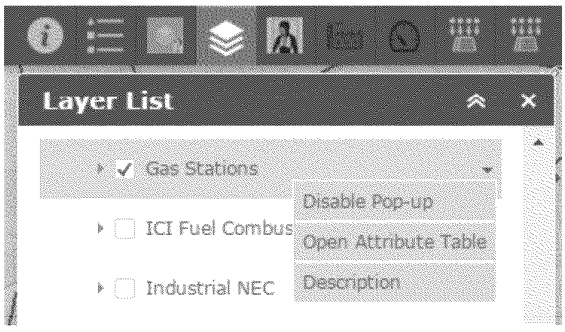




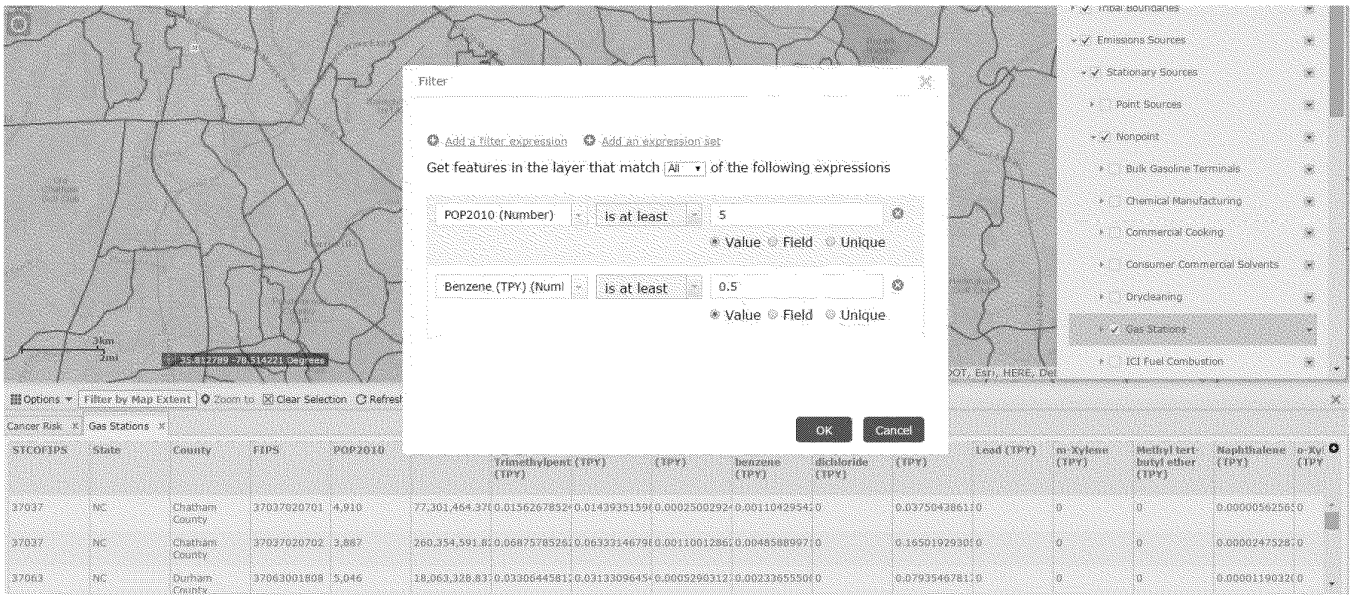
To run a query, select one of the query options, and choose the criteria by which you want to query the data. For example, below is a "By State/County and Risk" query of census tracts with total cancer risk of at least 50 in a million in Wake County, NC. A spatial filter has been used to limit the area over which the query willapply. The spatial filter can be a rectangular area as shown below or other shapes. The spatial filter can also be the current map extent (the first option under spatial filter). Finally, the box has been checked to add the query results as an operational layer in the map. This should always be checked so the results will be added to thelayer list and the attribute table of the results can be viewed.



Although there are not specific queries for all layers in the app, these layers can still be queried by opening the attribute table of the layer, and filtering the datausing criteria similar to those included in the specific queries in the app. For example, this is how to open the attribute table for the Gas Stations emissions layer:

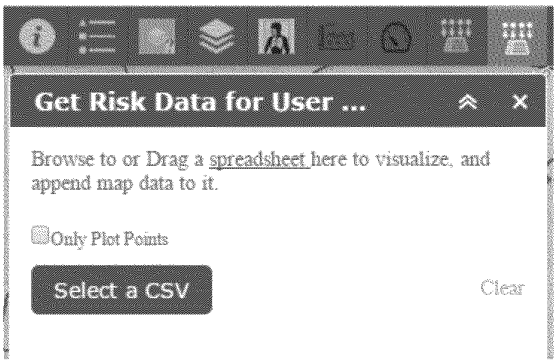


While in the attribute table, click on the "Options" dropdown and select "Filter". This is an example of a query of the Gas Stations data for census tracts with at least five people in them and with benzene emissions of at least 0.5 tons per year:



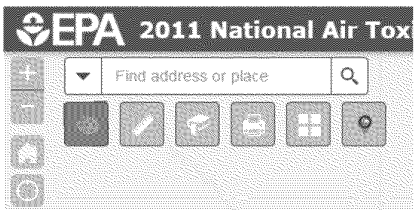
The results of the filter are not added as an operational layer as they are with the query widgets in the app, but the data can be viewed, sorted (by clicking on the field names), and downloaded (by selecting "Export All to CSV", under "Options"). Note that the maximum number of records that can be exported is 1000.

There is the option in the NATA App to input a user-supplied file of point locations and display those locations on the map. The coordinate field names that are recognized and can be plotted are lat, latitude, y, ycenter, and point_y (for latitude), and lon, long, longitude, x, xcenter, point_x (for longitude). There is also the ability to "enrich" the point locations with some of the data in the map, including risk and ambient concentration data. For example, if you wanted to plot the locations of schools and get the risk estimates for the census tracts that the schools are in, you would select your comma-separated value (CSV) file of school data by browsing for it or dragging and dropping on the widget window. The points would be plotted, and an operational layer of your results would be added to the layer list.



Other Widgets

Below is a description of other basic widgets that are available in the app.

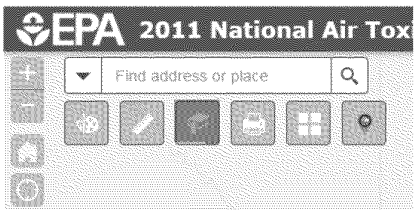


Draw Widget

The Draw widget enables users to draw basic graphics and text on the map. It provides basic sketching and redlining functionality for the web application. Note that when "Clear" is clicked, the widget removes all objects drawn and not just the most recently drawn.

Measurement Widget

The Measurement widget allows the user to measure the area of a polygon, length of a line, or find the coordinates of a point.



Bookmark Widget

The Bookmark widget enables users to save the map view extents of frequently viewed areas so as to easily go to those areas in the future. This could be useful for printing maps with consistent extents every time.

Print Widget

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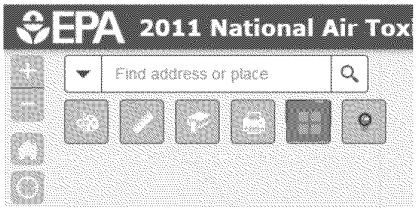

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Summary of Results for the 2011 National-Scale Assessment

INTRODUCTION

NATA is a prioritization tool. Its purpose is to identify geographic areas, pollutants and emission sources that should be evaluated further to gain a better understanding of risks. EPA uses NATA in many ways, including:

- To set priorities for improving data in emissions inventories
- To work with communities in designing their own local-scale assessments, and
- To help direct priorities for expanding and improving air toxics monitoring.

NATA helps state, local and tribal air agencies focus resources on geographic areas, pollutants and types of emission sources for closer investigation. Once risks are further characterized, agencies can determine steps to reduce air toxics emissions where necessary. NATA provides broad estimates of risk over geographic areas of the country and not definitive risks to specific individuals. This is because NATA uses models to estimate risks; it is not designed to determine actual risks. NATA is designed to prioritize pollutants and areas for further study, not to compare one area of the country's risk to another. This is because the emissions data underlying the assessment can vary in level of detail from state to state.

Of the 180 air toxics plus diesel PM included in the 2011 national-scale assessment, the risk characterization considers the risk of both cancer and noncancer effects from inhalation of 138 of these air toxics -- the subset of pollutants with health data based on chronic exposure. The purpose of this national-scale assessment is to understand these cancer risks and noncancer health effects in order to help the EPA and others to identify pollutants and source categories of greatest potential concern, and to set priorities for the collection of additional information to improve future assessments. The assessment represents a "snapshot" in time for characterizing risks from exposure to air toxics. The national-scale assessment is not designed to characterize risks sufficiently for it to be the sole source for regulatory action.

The 2011 national-scale risk assessment is based on a 2011 inventory of air toxics emissions (the most complete and up-to-date available). It then assumes individuals spend their entire lifetimes exposed to these air toxics. Therefore, it does not account for the reductions in emissions that have occurred since 2011 or those that will happen in the near future due to regulations for mobile and industrial sources. This risk assessment represents an update and enhancement to EPA's 2005 national-scale assessment. The next assessment will focus on emissions for the year 2014.

Note that in this assessment, the potential carcinogenic risk from diesel PM is not addressed because there currently is no unit risk estimate available. However, there are noncancer results. Learn more about EPA's qualitative assessment of diesel PM.

Given its broad scope, this risk characterization is subject to a number of limitations due to gaps in data or in the state of the science for assessing risk. For example, the current assessment does not include results for dioxins, compounds that may contribute substantially to risks. In addition, the EPA is reassessing the health effects of many pollutants considered in this study. A status report for all EPA health effect assessments is available from EPA's Integrated Risk Information System (IRIS). For more details on the limitations of the 2011 NATA, refer to the Results section on the NATA Web site.

The risk characterization, which was limited to inhalation risk from outdoor sources, was designed to answer the following questions:

1. Which air toxics pose the greatest potential risk of cancer or adverse noncancer effects across the entire United States?
2. Which air toxics pose the greatest potential risk of cancer or adverse noncancer effects in some areas of the United States?
3. Which air toxics pose lesser, but still significant, potential risk of cancer or adverse noncancer effects across the entire United States?
4. When risks from all air toxics are combined, how many people have the potential for an upper-bound lifetime cancer risk greater than 10-in-1 million?
5. When potential adverse respiratory or neurological effects from all air toxics are combined, how many people have the potential for exposures that exceed reference levels intended to protect against adverse effects, i.e., a target organ-specific hazard index greater than 1.0?

For general background on risk characterization, see the discussion in questions and answers format on this topic.

SUMMARY OF RESULTS

Based on a comparison of the cancer and noncancer risks estimated for the 138 air toxics quantified by the 2011 national-scale assessment, it is possible to determine which air toxics pose the greatest potential risk in the United States. A summary of these findings are reported below. Cancer risks in this assessment are presented as lifetime risks, meaning the risk of developing cancer as a result of exposure to each air toxic compound over a normal lifetime of 70 years. Noncancer risks are presented in terms of the ratio between the exposure and a reference concentration. This ratio is called the hazard quotient. The risk characterization summary below focuses on results at the national level, where the EPA believes the results are most meaningful.

To help understand the results, it should be noted that:

- Concentration results (ambient and exposure) are provided for 180 air toxics plus diesel PM
- Cancer results are presented for 71 air toxics that have quantitative dose-response information

- Noncancer results are presented for 112 air toxics with quantitative dose-response information
- Many noncancer reference concentrations incorporate protective assumptions designed to provide a margin of safety. A hazard quotient greater than one does not necessarily suggest a likelihood of adverse effects. A hazard quotient equal to or less than one, however, suggests that exposures are likely to be without an appreciable risk of noncancer effects during a lifetime. Furthermore, the hazard quotient cannot be translated into a probability that an adverse effect will occur, and is not proportional to risk

The following conclusions on individual air toxics compounds were drawn from the risk characterization.

The following table presents the criteria for classifying the 2011 NATA air toxics and will be helpful in understanding the conclusions below. In general, drivers and contributors are defined as air toxics showing a particular level of risk or hazard for some number of people exposed.

2011 NATA Health Effects Drivers and Contributors Risk Characterization

Risk Characterization Category	**Risk Exceeds (in 1 million)[1]**	**HI > 1.0[2]**	**Number of People or Greater Exposed (in millions)**
National Cancer Driver	10		25
Regional Cancer Driver	10		1
Regional Cancer Driver	100		0.01
National Cancer Contributor	1		25
Regional Cancer Contributor	1		1
National Noncancer Driver		1.0	25
Regional Noncancer Driver		1.0	0.01

[1]Cancer risks are upper-bound lifetime cancer risks (i.e., a plausible upper limit to the true probability that an individual will contract cancer over a 70 year lifetime as a result of a given hazard (such as exposure to a toxic chemical). This risk can be measured or estimated in numerical terms (e.g., one chance in one million).

[2]HI = the sum of hazard quotients for substances that affect the same target organ or organ system. Because different pollutants may cause similar adverse health effects, it is often appropriate to combine hazard quotients associated with different substances to understand the potential health risks associated with aggregate exposures to multiple pollutants.

- **National cancer risk driver**: Formaldehyde
- **Regional cancer risk drivers**: Benzene, Chloroprene, Coke Oven Emissions

- **National cancer risk contributors**: 1,3-Butadiene, Acetaldehyde, Carbon tetrachloride, Chromium (VI), Ethylbenzene, Naphthalene
- **Regional cancer risk contributors**: 1,3-Dichloropropene, 1,4-Dichlorobenzene, Arsenic compounds, Ethylene oxide, Nickel compounds, PAH/POM

- **National noncancer hazard drivers**: Acrolein, Chlorine, Diesel PM
- **Regional noncancer hazard drivers**: Hexamethylene diisocyanate

Health Effects of National Air Toxic Drivers

Cancer Risk Drivers

Formaldehyde - Acute (short term) and chronic (long term) exposures have been shown to cause respiratory symptoms and irritation to the eyes, nose, and throat. Human studies have suggested an association between formaldehyde exposure and lung and nasopharyngeal cancer. Studies in animals have reported an increased incidence of nasal squamous cell cancer. EPA considers formaldehyde "likely to be carcinogenic to humans".

Noncancer Drivers

Acrolein - It is toxic to humans following inhalation, oral or dermal exposures. Acute and chronic inhalation exposure may result in eye, nose and throat irritation and respiratory tract congestion. EPA considers the existing acrolein data to be inadequate for assessing human carcinogenic potential.

Chlorine – Acute (short term) and chronic (long term) exposure has been shown to cause irritation to the eyes, upper respiratory tract and lungs. Studies on workers in the chemical industry and experimental studies in animals have not reported evidence of carcinogenic effects from exposure to chlorine. EPA has not classified chlorine for potential carcinogenicity.

Diesel exhaust (including diesel PM) – Acute (short term) exposures can cause irritation (e.g., eye, throat), neurophysiological symptoms (e.g., lightheadedness, nausea), and respiratory symptoms (e.g., cough, phlegm). Chronic (long term) exposures may lead to inflammation and changes in the lung. EPA considers diesel exhaust "likely to be carcinogenic to humans by inhalation" but at this time does not have a quantitative characterization of cancer risk.

The following conclusions on simultaneous exposure to all air toxics compounds were drawn from the risk characterization.

Cumulative Cancer Risks:

NATA estimates that all 285 million people in the U.S. have an increased cancer risk of greater than 10 in one million. Half a million people (less than 1 percent of the total U.S. population based on the 2010 census) have an increased cancer risk of greater than 100 in a million. The average, national, cancer risk for 2011 is 40-in-1 million. This means that, on average, approximately 1 in every 25,000 people have an increased likelihood of contracting cancer as a

result of breathing air toxics from outdoor sources if they were exposed to 2011 emission levels over the course of their lifetime

Cumulative Noncancer Hazards:
Ideally, hazard quotients should be combined for pollutants that cause the same adverse effects by the same toxic mechanism. For the 2011 NATA assessment, we present results for HAP that act by similar modes of action, or (where this information is absent) that affect the same target organ. This process creates, for each target organ, a target-organ-specific hazard index, defined as the sum of hazard quotients for individual HAP that affect the same organ or organ system. For the 2011 NATA, the hazard indices for the respiratory system dominate the results.

The respiratory hazard index was dominated by a single substance, acrolein, which contributed about 70 percent of the nationwide average non-cancer hazard. The respiratory hazard index exceeded 1.0 for approximately 170 million people while the HI exceeded 10 for more than 75,000 people.

2011 NATA Web Application

Results can also be viewed on maps using EPA's Web application. Using the web app mapping tool, the user can generate maps showing geographic patterns of estimated cancer and non-cancer risks in 2011 from inhalation of air toxics. These maps represent a snapshot of conditions in 2011 and are not reflective of current conditions. EPA developed this GIS tool for the 2011 NATA to inform both national and more localized efforts to collect air toxics information and characterize emissions (e.g., prioritize pollutants/geographic areas of interest for more refined data collection such as monitoring). These maps are for screening purposes only. EPA suggests caution in interpreting the information displayed, as limitations and uncertainties of the assessment will vary from location to location as well as from pollutant to pollutant. In many cases more localized assessments, including monitoring and modeling, may be needed to better characterize local-level risk.

Prioritization of Louisiana Parishes based on Industrial Releases of Known or Suspected Carcinogens

Adrienne Katner, MS, DEnv

This investigation evaluated the geographic distribution of carcinogen releases by Louisiana industries to prioritize areas for regulatory oversight, research and monitoring, and to promote clinician awareness and vigilance. Data on estimated industry releases for the period between 1996 and 2011 were obtained from the US Environmental Protection Agency's Toxics Release Inventory. Chemicals associated with cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were identified. The Risk Screening Environmental Indicators model was used to derive measures or model scores based on chemical toxicity, fate and transport, and population characteristics. Parishes, chemicals, industries and media generating the highest model scores were identified. Parishes with the highest model scores were East Baton Rouge, Calcasieu, Caddo and St. John the Baptist. Clinicians should carefully monitor cancer cases in these areas, and if patients reside near or work in industry, an occupational and environmental history should be considered.

INTRODUCTION

In Louisiana, cancer incidence is significantly higher than the national rate for white men, black men and black women; and cancer mortality is significantly higher for blacks and whites of both sexes.[1] The reasons for these disparities are not fully understood,[1] but may include factors such as genetic predisposition, behavioral influences like smoking, access to medical care or early screening, and environmental hazard exposures. Environmental and occupational exposures have been estimated to contribute to only 6 percent of all cancer deaths in the US.[2] However, an accurate measure of the contribution of these factors to cancer risk is impossible, as the causes of cancer can be difficult to identify and may be multifactorial.[3-5] While there is little doubt that lifestyle factors such as smoking, physical inactivity, poor nutrition and obesity are the most important contributors to cancer when compared to environmental or occupational exposures, lower income workers and communities may have disproportionately higher exposures to occupational and environmental carcinogens.[6] Therefore, clinicians should be aware of the types of industrial hazards that may be present in their communities.

Most industries have been required to report toxic environmental releases to the US Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI) Program since 1988. These facilities include those that meet the following conditions: 1) employ 10 or more full time workers; and 2) are in a specific industrial sector or are a federal facility; and 3) manufacture or process more than 25,000 pounds of a listed chemical or uses more than 10,000 pounds of a listed chemical in a given year.[7] Over 682 chemicals and chemical categories must be reported along with information describing the facility, the chemical released, the release amount and the media of release.[7] TRI data on chemical releases have proved useful to public health surveillance and research activities.[8-9] For example, areas with higher levels of TRI releases are significantly associated with higher mortality rates.[8] Areas with higher levels of TRI-reported carcinogen releases are associated with significantly higher hospitalization rates.[9] And a significantly increased risk of lung cancer incidence has been associated with TRI releases of chromium, formaldehyde and nickel.[10] Studies of this kind have been useful in generating hypotheses and stimulating research, but like all ecological studies, they are prone ecological fallacy. They merely demonstrate association, not causation, because of unmeasured and uncontrolled confounding factors.

Several studies have used TRI data to identify areas and populations facing the highest potential health risks from industrial releases.[11-13] Most previous studies have relied on quantity-based evaluations, but did not account for factors such as chemical toxicity, environmental fate and transport, or population proximity and characteristics. In 2004, Chakraborty[11] was one of the first researchers to incorporate Toxic Equivalency Potentials, a crude measure of potential harm based on toxicity and environmental fate, into a TRI-based screening study to identify states facing

the highest potential carcinogenic and non-carcinogenic risk from industrial toxic releases. And in 2010, Lim *et al*[12] coupled TRI data with toxicity potentials to rank and prioritize chemicals, states and industries. Both of these nationwide studies identified Louisiana as one of the ten states with the highest potential cancer impact from TRI releases.

This investigation extends those two prior studies but narrows the focus to Louisiana parishes and bases the screening on a novel measure. The US EPA's Risk Screening Environmental Indicators (RSEI) model is used to derive chemical- and facility-specific scores. The RSEI model estimates a surrogate "dose" based on chemical-specific reported release quantities, pathway-specific modeling of the chemical fate and transport through the environment, and facility-specific population characteristics and exposure factors.[14-15] It then incorporates toxicity information to calculate a relative "risk" score for the entire population.[15] The RSEI-based score is not a true risk estimation- it is a unitless measure and is not independently meaningful. Rather, it is a relative measure that can be compared to other RSEI-based scores to compare and prioritize areas, chemicals and industries.[14] In this study, model scores were generated for groups of chemicals with known or suspected associations to specific cancers. Cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were selected on the basis of their high state incidence rates[1] and their association with environmental hazards in the literature. These cancer-specific scores were then used to prioritize parishes and industries. Rankings are intended to serve as a guide to direct local research or monitoring investigations, and promote clinician awareness and vigilance. It should be emphasized that the information provided here is for screening purposes only and must not be construed to imply any causal relationship between a release and an individual case of disease. Cancer incidence rates were not purposefully included to prevent unintended linkages with these derived scores, as that is not the objective of this analysis. Cancer incidence rates can be obtained from the Louisiana Tumor Registry's website.[1] The results highlighted serve only as a starting point for drawing attention to areas that have the potential for health impact due to industrial toxic releases.

MATERIALS AND METHODS

Environmental releases of carcinogens reported to the TRI Program between 1996 and 2011 were evaluated. Occupational Safety and Health Administration (OSHA) carcinogens and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and with non-Hodgkin lymphoma (NHL) were the focus of this investigation. Several sources were used to create a list of chemicals considered to be known or suspected carcinogens. These included the International Agency for Research on Cancer (IARC),[16] the EPA's Integrated Risk Screening Information System (IRIS),[17] the National Toxicology Program's 12th Report on Carcinogens,[18] and the OSHA Select Carcinogen list.[19] Table 1 presents the list of chemicals evaluated.

Technical information about the methodology and assumptions used in the RSEI model for calculating relative scores for releases and transfers to air and water are available online.[14] Release estimates (pounds), which are values directly reported to the TRI program based on facility calculations, were also obtained using the RSEI model. The sum of releases and model scores were derived for cancer-specific carcinogens by chemical, medium of release (only air and water releases were evaluated), industry (based on 2-digit primary standard industrial classification or code or SIC) and parish. Aggregate releases and model scores were then ranked to prioritize chemicals, media, industries and parishes.

RESULTS

Model scores were used to prioritize parishes releasing OSHA carcinogens, and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and non-Hodgkins lymphoma (NHL) (Table 2). Figure 1 presents the percent of parish contribution to the total state model score for cancer-specific carcinogens. Parishes consistently ranked as the highest contributors to statewide model scores included: Caddo, St. John the Baptist, East Baton Rouge and Calcasieu. These parishes were also along the highest contributors to statewide model scores for OSHA carcinogens.

Carcinogens contributing the greatest amounts to the total statewide cancer-specific model scores included: chromium, polycyclic aromatic compounds and 1,3-butadiene. Other high carcinogen contributors to the total model scores included: chloroprene, chloroform, trichloroethylene, benzene, and lead and lead compounds (Table 2). Many of these chemicals with the largest model scores were not among those with the largest releases (data not shown), highlighting the impact that other factors, such as chemical fate and transport, play in the potential for exposure and health impact.

Industries contributing the greatest amounts to the total statewide cancer-specific model scores included: chemicals and allied products, fabricated metal products, and petroleum refining and related industries (Table 2). In Calcasieu Parish, 99% of TRI-reporting facilities are industries within the categories of chemicals and allied products or petroleum refining and related industries. These industries also account for 99.6% of TRI-reporting facilities in East Baton Rouge Parish. In Caddo Parish, 'fabricated metal products' comprise about 99.5% of TRI-reporting facilities; and in St. John the Baptist Parish, 'chemicals and allied products' comprise about 99.6% of TRI-reporting facilities.

The media of release contributing the greatest to the total statewide model scores for most cancer-specific carcinogen groups were fugitive air emissions and point (or stack) air

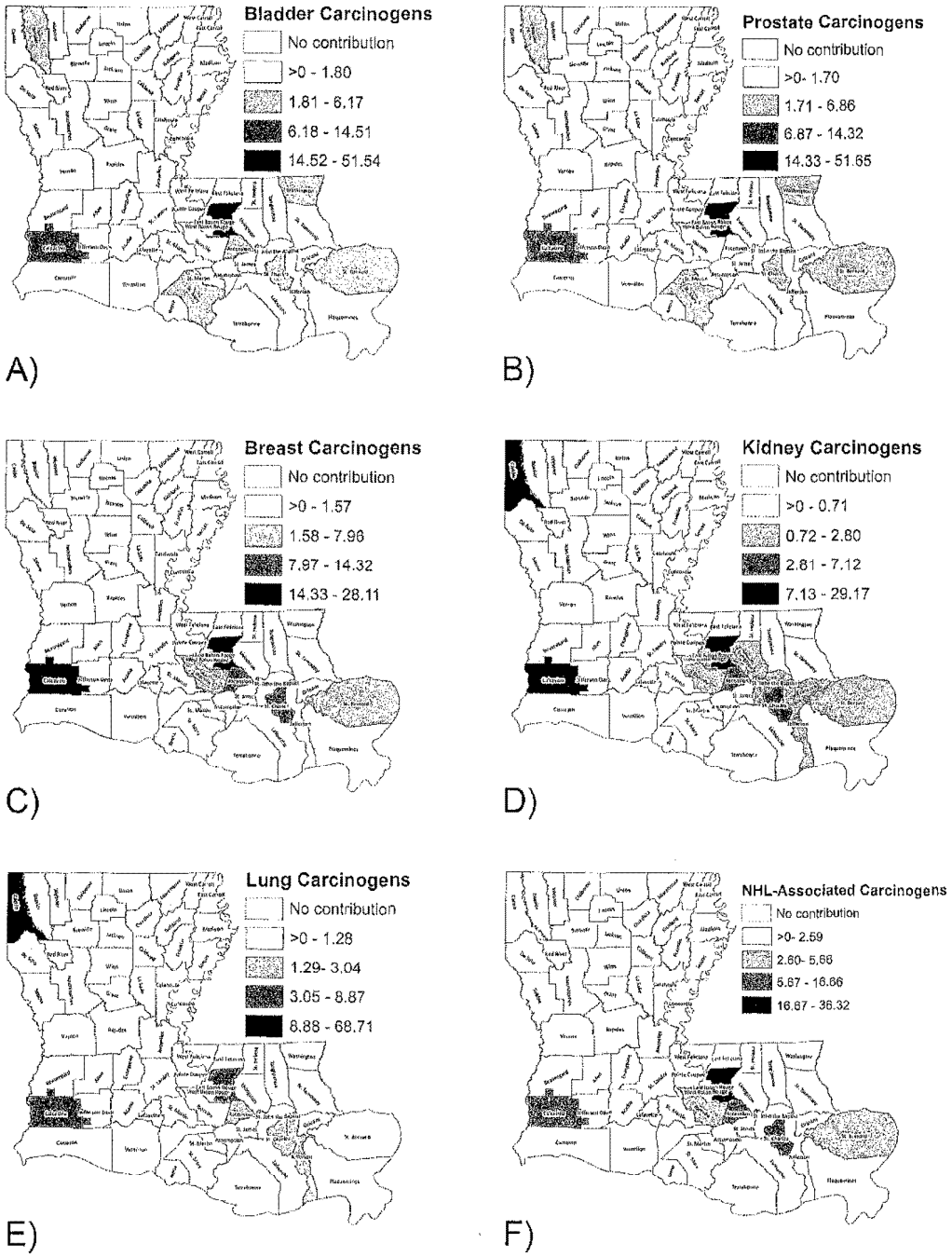
Table 1: List of cancer-specific carcinogens reported to the EPA's TRI Program and included in the evaluation

OSHA Carcinogens	OSHA Carcinogens (continued)	Breast-Associated Carcinogens	NHL-Associated Carcinogens	Kidney-Associated Carcinogens (continued)
1,1-Dimethyl Hydrazine	Diethyl sulfate	1,2-Dichloroethane	1,2-Dichloroethane	Tetrachloroethylene
1,2,3-Trichloropropane	Dimethyl sulfate	1,3-Butadiene	1,3-Butadiene	Trichloroethylene
1,2-Butylene oxide	Dioxane	Acetaldehyde	Acetaldehyde	**Bladder-Associated Carcinogens**
1,2-Dibromoethane	Dioxin and dioxin-like compounds	Benzene	Arsenic & arsenic compounds	Arsenic and arsenic compounds
1,2-Dichloroethane	Epichlorohydrin	Carbon tetrachloride	Benzene	Cadmium & Cd compounds
1,3-Butadiene	Ethyl acrylate	Dichloromethane	Cadmium & Cd compounds	Cadmium & Cd compounds
1,3-Dichloropropylene	Ethylbenzene	Dioxane	Carbon tetrachloride	Chloroform
2,4-Diaminotoluene	Ethylene oxide	Hydrazine	Formaldehyde	Creosote, coal tar
2,4-Dinitrotoluene	Formaldehyde	Nitrobenzene	Hexachlorobenzene	Dichlorobromomethane
2,6-Xylidine	Glycidol	Polychlorinated biphenyls (PCBs)	Lead and lead compounds	Lead and lead compounds
2-Nitropropane	Heptachlor	Propyleneimine	Polychlorinated biphenyl (PCBs)	Polycyclic aromatic compounds
4,4'-Methylenedianiline	Hexachlorobenzene	Styrene	Polycyclic aromatic compounds	Tetrachloroethylene
4-Aminoazobenzene	Hexachloroethane	Toluenediisocyanate	Styrene	
4-Aminodiphenyl	Lead and lead compounds	**Lung-Associated Carcinogens**	Tetrachloroethylene	
Acetaldehyde	Naphthalene	1,2-Dichloroethane	Trichloroethylene	
Acetamide	Nickel and nickel compounds	1,3-Butadiene	**Prostate-Assoc. Carcinogens**	
Acrylamide	Nitrilotriacetic acid	Acetaldehyde	Arsenic & arsenic compounds	
Acrylonitrile	Nitrobenzene	Acrylamide	Cadmium & Cd compounds	
Arsenic and arsenic compounds	Nitromethane	Acrylonitrile	Creosote, coal tar	
Asbestos (friable)	o-Toluidine	Arsenic and arsenic compounds	Dichloromethane	
Benzene	Pentachlorophenol	Benzene	Dioxin & dioxin-like compounds	
Beryllium and beryllium compounds	Polychlorinated biphenyls	Cadmium & Cd compounds	Polycyclic aromatic compounds	
Cadmium and cadmium compounds	Polycyclic aromatic compounds	Chromium & Cr compounds	Trichloroethylene	
Carbon tetrachloride	Propylene oxide	Creosote, coal tar	**Kidney-Associated Carcinogens**	
Catechol	Propyleneimine	Dichloromethane	1,3-Butadiene	
Chlordane	Styrene	Dioxin and dioxin-like compounds	1,4-Dichlorobenzene	
Chloroform	Styrene oxide	Epichlorohydrin	Acrylamide	
Chloroprene	Tetrachloroethylene	Ethylene oxide	Arsenic and arsenic compounds	
Chromium and chromium compounds	Toluene-2,4-diisocyanate	Formaldehyde	Cadmium & Cd compounds	
Cobalt and cobalt compounds	Toluenediisocyanate	Hydrazine	Chloroform	
Creosote, coal tar	Toxaphene	Lead and lead compounds	Creosote, coal tar	
Di(2-ethylhexyl) phthalate	trans-1,3-Dichloropropene	Nickel and nickel compounds	Dichloromethane	
Di(2-ethylhexyl) phthalate	Trichloroethylene	Nitrobenzene	Dioxane	
Diaminotoluene (mixed isomers)	Urethane (Ethyl carbamate)	Polychlorinated biphenyls (PCBs)	Dioxin & dioxin-like compounds	
Dichlorobenzene (mixed isomers)	Vinyl acetate	Polycyclic aromatic compounds	Hexachlorobenzene	
Dichlorobromomethane	Vinyl bromide	Styrene	Lead and lead compounds	
Dichloromethane	Vinyl chloride	Sulfuric acid	Nickel and nickel compounds	

Table 2: Top contributors to total model scores (% of contribution to total score)

	OSHA carcinogens	Bladder carcinogens	Prostate carcinogens	Breast carcinogens	Kidney carcinogens	Lung carcinogens	NHL-associated carcinogens
Parishes	Caddo (43%)[1]	East Baton Rouge (52%)[3]	East Baton Rouge (52%)[5]	Calcasieu (28%)[7]	East Baton Rouge (29%)[9]	Caddo (69%)[11]	East Baton Rouge (36%)[13]
	St. John the Baptist (24%)[2]	Calcasieu (15%)[4]	Calcasieu (14%)[6]	East Baton Rouge (23%)[8]	Calcasieu (22%)[10]	East Baton Rouge (9%)[12]	Calcasieu (17%)[14]
Chemicals	Chromium and chromium compounds (44%)	Polycyclic aromatic compounds (84%)	Polycyclic aromatic compounds (94%)	1,3-Butadiene (23%)	1,3-Butadiene (42%)	Chromium and chromium compounds (71%)	Polycyclic aromatic compounds (35%)
	Chloroprene (24%)	Chloroform (12%)	Trichloroethylene (3%)	Benzene (23%)	Lead and lead compounds (28%)	Polycyclic aromatic compounds (7%)	1,3-Butadiene (16%)
Industries	Chemicals and allied products (71%)	Chemicals and allied products (61%)	Chemicals and allied products (57%)	Chemicals and allied products (75%)	Chemicals and allied products (48%)	Fabricated metal products (70%)	Chemicals and allied products (66%)
	Fabricated metal products (2%)	Petroleum refining and related industries (27%)	Petroleum refining and related industries (31%)	Petroleum refining and related industries (18%)	Fabricated metal products (24%)	Chemicals and allied products (17%)	Petroleum refining and related industries (25%)
Media	Fugitive air emissions (59%)	Direct water releases (53%)	Direct water releases (53%)	Fugitive air emissions (58%)	Fugitive air emissions (89%)	Fugitive air emissions (83%)	Fugitive air emissions (43%)
	Point (stack) air emissions (37%)	Fugitive air emissions (23%)	Fugitive air emissions (23%)	Point (stack) air emissions (39%)	Point (stack) air emissions (10%)	Point (stack) air emissions (12%)	Point (stack) air emissions (33%)

Figure 1: Percent of parish contribution to total statewide model score for cancer-specific carcinogens (based on 1996-2011 TRI-reported data and RSEI-generated scores).



Note: Data are displayed using the Jenks Optimization (Natural Breaks) method of classification

emissions. However, for bladder and prostate carcinogens, direct water releases were a primary contributor to total statewide model scores, and fugitive air emissions were a secondary contributor (Table 2).

DISCUSSION

According to Louisiana's Division of Administration, Louisiana "has the greatest concentration of crude oil refineries, natural gas processing plants and petrochemical facilities in the Western Hemisphere".[20] In addition, "Louisiana produces 25 percent of the nation's petrochemicals"; is the third largest producer and refiner of petroleum; and has "more than 100 major chemical plants " producing "chemicals, fertilizers and plastics, plus the feedstocks for a wide array of other products". [20] Many of the parishes identified in this investigation are consistently ranked as top contributors to the model scores (Figure 1). This is to be expected as they are among the most heavily industrialized areas of the state. With the exception of St. John the Baptist Parish, each identified parish has over 25 TRI-reporting facilities: Calcaiseu has 42 facilities (8% of the state's TRI-reporting facilities), East Baton Rouge has 40 facilities (7%), and Caddo has 26 facilities (5%), while St. John the Baptist has only 13 facilities (2%). Given the extent of industrial activities in the state, awareness of the distribution of potential hazards is essential in order to both recognize and prevent diseases associated with occupational and environmental exposures.

It is the intent of the author to motivate clinicians, especially environmental and occupational health professionals, to investigate the RSEI model for the purpose of screening their communities for potential hazards caused by industrial releases. The RSEI model allows those who want to evaluate the potential impact of TRI releases, to screen locations and facilities based on a measure which incorporates exposure and toxicity factors. The RSEI models exposure pathways for stack and fugitive air emissions, direct surface water releases, transfers to publically owned treatment works, off site transfers and on-site land releases; and calculates risk-related results for air and surface water pathways.[15] The models, parameters, algorithms and assumptions used to estimate exposure are too lengthy to list here, but are described in detail in EPA's technical documentation.[15] As with all models, results are based on simplified inputs, such as those measuring toxicity, environmental fate and transport, and potential exposure. Air pathways were modeled using the American Meteorological Society/EPA Regulatory Model (AERMOD)- a steady state Gaussian plume model used to estimate pollutant concentrations downwind of a stack or area source. Facility-specific parameters, meteorology and chemical-specific first order decay rates are used. Surface water pathways are modeled by estimating contaminant concentrations in drinking water and fish, where a public water system's intake is located in a stream path of the release. Some data used in surface water models include EPA's records of discharge permits, decay coefficients, estimates of water velocity, public water system distribution details from EPA's Safe Drinking Water Information System and chemical-specific bioconcentration factors. [15] The sources for exposure factors, toxicity weights and demographics are the EPA's Exposure Factors Handbook,[21] EPA's Integrated Risk Information System,[17] and the US Census data, respectively. As stated in EPA's RSEI methodology document, [15] "The exposure algorithms are intended to be simple ways to gauge relative risks from releases to different media in a consistent, defensible way, by modeling and estimating exposure. In some cases, the modeling is purposely simplified, given the lack of site-specific data". In short, the RSEI is a free and simple to use model that can assist clinicians in local investigations, when the causal factor of a disease is unknown, or when environmental exposure factors are suspected.

Results presented are subject to several limitations due to the availability and quality of model inputs and model assumptions. For example, not all sources of carcinogens are included in this analysis- mobile sources and industries under the reporting threshold are not represented; and some carcinogens are not reported to the TRI Program. Also, model scores could not be generated for chemicals lacking information required for modeling, such as measures of toxicity. Probably the greatest limitation is that industry-reported TRI data are hard to verify and may be prone to biased reporting. One cannot exclude the possibility that industries under-report actual releases to meet regulatory requirements. Results should also be put into the proper context. That is, this analysis does not consider chemicals that people are exposed to on a more common basis. Toxicants can be found in vehicle exhaust, processed food, air fresheners, pesticides, paints and varnishes, and cleaning products, just to name a few sources. It is estimated that the average American spends 90 percent of their time indoors. Indoor pollutant levels may be two to five times higher than outdoor pollutant levels.[22] Thus, the RSEI model is most suitable for use by environmental and occupational clinicians to identify and screen potential hazards to workers and members of fenceline communities.

CONCLUSIONS

Caddo, St. John the Baptist, East Baton Rouge and Calcasieu parishes were consistently ranked as the highest contributors to cancer-specific model scores. Clinicians should be cognizant of industrial hazards in their communities, and conduct environmental and occupational histories of patients in fenceline communities or in industrial occupations. The RSEI model is an easy to use method for screening potential industry-related hazards at the parish or neighborhood level; and is relevant to doctors serving industry workers and fenceline communities. It is intended that the results presented here will guide and influence state monitoring efforts, regulatory oversight, health

investigations, and clinician awareness.

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Prioritization of Louisiana Parishes based on Industrial Releases of Known or Suspected Carcinogens

Adrienne Katner, MS, DEnv

This investigation evaluated the geographic distribution of carcinogen releases by Louisiana industries to prioritize areas for regulatory oversight, research and monitoring, and to promote clinician awareness and vigilance. Data on estimated industry releases for the period between 1996 and 2011 were obtained from the US Environmental Protection Agency's Toxics Release Inventory. Chemicals associated with cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were identified. The Risk Screening Environmental Indicators model was used to derive measures or model scores based on chemical toxicity, fate and transport, and population characteristics. Parishes, chemicals, industries and media generating the highest model scores were identified. Parishes with the highest model scores were East Baton Rouge, Calcasieu, Caddo and St. John the Baptist. Clinicians should carefully monitor cancer cases in these areas, and if patients reside near or work in industry, an occupational and environmental history should be considered.

INTRODUCTION

In Louisiana, cancer incidence is significantly higher than the national rate for white men, black men and black women; and cancer mortality is significantly higher for blacks and whites of both sexes.[1] The reasons for these disparities are not fully understood,[1] but may include factors such as genetic predisposition, behavioral influences like smoking, access to medical care or early screening, and environmental hazard exposures. Environmental and occupational exposures have been estimated to contribute to only 6 percent of all cancer deaths in the US.[2] However, an accurate measure of the contribution of these factors to cancer risk is impossible, as the causes of cancer can be difficult to identify and may be multifactorial.[3-5] While there is little doubt that lifestyle factors such as smoking, physical inactivity, poor nutrition and obesity are the most important contributors to cancer when compared to environmental or occupational exposures, lower income workers and communities may have disproportionately higher exposures to occupational and environmental carcinogens.[6] Therefore, clinicians should be aware of the types of industrial hazards that may be present in their communities.

Most industries have been required to report toxic environmental releases to the US Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI) Program since 1988. These facilities include those that meet the following conditions: 1) employ 10 or more full time workers; and 2) are in a specific industrial sector or are a federal facility; and 3) manufacture or process more than 25,000 pounds of a listed chemical or uses more than 10,000 pounds of a listed chemical in a given year.[7] Over 682 chemicals and chemical categories must be reported along with information describing the facility, the chemical released, the release amount and the media of release.[7] TRI data on chemical releases have proved useful to public health surveillance and research activities.[8-9] For example, areas with higher levels of TRI releases are significantly associated with higher mortality rates.[8] Areas with higher levels of TRI-reported carcinogen releases are associated with significantly higher hospitalization rates.[9] And a significantly increased risk of lung cancer incidence has been associated with TRI releases of chromium, formaldehyde and nickel.[10] Studies of this kind have been useful in generating hypotheses and stimulating research, but like all ecological studies, they are prone ecological fallacy. They merely demonstrate association, not causation, because of unmeasured and uncontrolled confounding factors.

Several studies have used TRI data to identify areas and populations facing the highest potential health risks from industrial releases.[11-13] Most previous studies have relied on quantity-based evaluations, but did not account for factors such as chemical toxicity, environmental fate and transport, or population proximity and characteristics. In 2004, Chakraborty[11] was one of the first researchers to incorporate Toxic Equivalency Potentials, a crude measure of potential harm based on toxicity and environmental fate, into a TRI-based screening study to identify states facing

the highest potential carcinogenic and non-carcinogenic risk from industrial toxic releases. And in 2010, Lim *et al*[12] coupled TRI data with toxicity potentials to rank and prioritize chemicals, states and industries. Both of these nationwide studies identified Louisiana as one of the ten states with the highest potential cancer impact from TRI releases.

This investigation extends those two prior studies but narrows the focus to Louisiana parishes and bases the screening on a novel measure. The US EPA's Risk Screening Environmental Indicators (RSEI) model is used to derive chemical- and facility-specific scores. The RSEI model estimates a surrogate "dose" based on chemical-specific reported release quantities, pathway-specific modeling of the chemical fate and transport through the environment, and facility-specific population characteristics and exposure factors.[14-15] It then incorporates toxicity information to calculate a relative "risk" score for the entire population.[15] The RSEI-based score is not a true risk estimation- it is a unitless measure and is not independently meaningful. Rather, it is a relative measure that can be compared to other RSEI-based scores to compare and prioritize areas, chemicals and industries.[14] In this study, model scores were generated for groups of chemicals with known or suspected associations to specific cancers. Cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were selected on the basis of their high state incidence rates[1] and their association with environmental hazards in the literature. These cancer-specific scores were then used to prioritize parishes and industries. Rankings are intended to serve as a guide to direct local research or monitoring investigations, and promote clinician awareness and vigilance. It should be emphasized that the information provided here is for screening purposes only and must not be construed to imply any causal relationship between a release and an individual case of disease. Cancer incidence rates were not purposefully included to prevent unintended linkages with these derived scores, as that is not the objective of this analysis. Cancer incidence rates can be obtained from the Louisiana Tumor Registry's website.[1] The results highlighted serve only as a starting point for drawing attention to areas that have the potential for health impact due to industrial toxic releases.

MATERIALS AND METHODS

Environmental releases of carcinogens reported to the TRI Program between 1996 and 2011 were evaluated. Occupational Safety and Health Administration (OSHA) carcinogens and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and with non-Hodgkin lymphoma (NHL) were the focus of this investigation. Several sources were used to create a list of chemicals considered to be known or suspected carcinogens. These included the International Agency for Research on Cancer (IARC),[16] the EPA's Integrated Risk Screening Information System (IRIS),[17] the National Toxicology Program's 12th Report on Carcinogens,[18] and the OSHA Select Carcinogen list.[19] Table 1 presents the list of chemicals evaluated.

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RESULTS

Model scores were used to prioritize parishes releasing OSHA carcinogens, and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and non-Hodgkins lymphoma (NHL) (Table 2). Figure 1 presents the percent of parish contribution to the total state model score for cancer-specific carcinogens. Parishes consistently ranked as the highest contributors to statewide model scores included: Caddo, St. John the Baptist, East Baton Rouge and Calcasieu. These parishes were also along the highest contributors to statewide model scores for OSHA carcinogens.

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Table 1: List of cancer-specific carcinogens reported to the EPA's TRI Program and included in the evaluation

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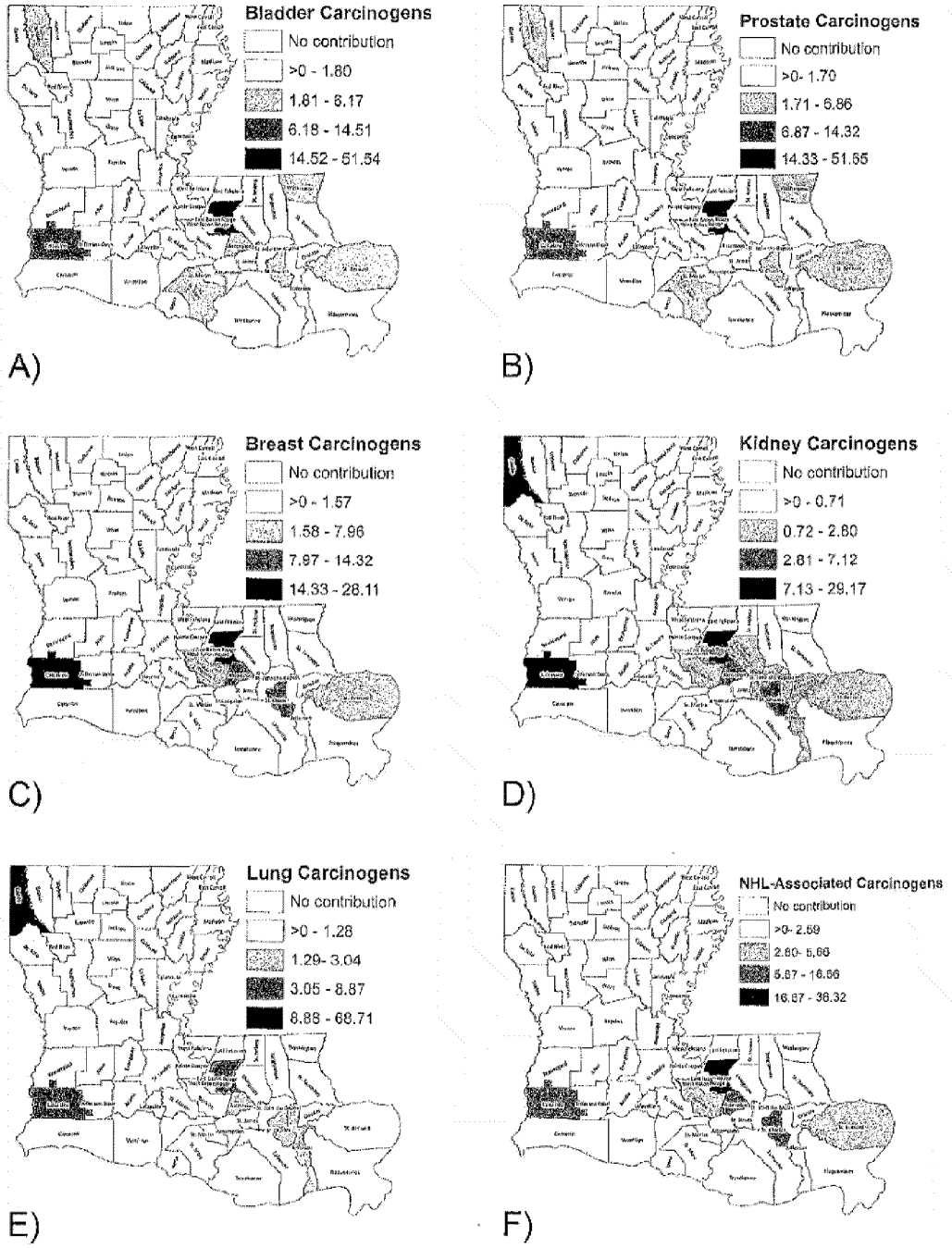
1,1-Dimethyl Hydrazine	Diethyl sulfate	1,2-Dichloroethane	1,2-Dichloroethane	Tetrachloroethylene
1,2,3-Trichloropropane	Dimethyl sulfate	1,3-Butadiene	1,3-Butadiene	Trichloroethylene
1,2-Butylene oxide	Dioxane	Acetaldehyde	Acetaldehyde	**Bladder-Associated Carcinogens**
1,2-Dibromoethane	Dioxin and dioxin-like compounds	Benzene	Arsenic & arsenic compounds	Arsenic and arsenic compounds
1,2-Dichloroethane	Epichlorohydrin	Carbon tetrachloride	Benzene	Cadmium & Cd compounds
1,3-Butadiene	Ethyl acrylate	Dichloromethane	Cadmium & Cd compounds	Cadmium & Cd compounds
1,3-Dichloropropylene	Ethylbenzene	Dioxane	Carbon tetrachloride	Chloroform
2,4-Diaminotoluene	Ethylene oxide	Hydrazine	Formaldehyde	Creosote, coal tar
2,4-Dinitrotoluene	Formaldehyde	Nitrobenzene	Hexachlorobenzene	Dichlorobromomethane
2,6-Xylidine	Glycidol	Polychlorinated biphenyls (PCBs)	Lead and lead compounds	Lead and lead compounds
2-Nitropropane	Heptachlor	Propyleneimine	Polychlorinated biphenyl (PCBs)	Polycyclic aromatic compounds
4,4'-Methylenedianiline	Hexachlorobenzene	Styrene	Polycyclic aromatic compounds	Tetrachloroethylene
4-Aminoazobenzene	Hexachloroethane	Toluenediisocyanate	Styrene	
4-Aminodiphenyl	Lead and lead compounds	**Lung-Associated Carcinogens**	Tetrachloroethylene	
Acetaldehyde	Naphthalene	1,2-Dichloroethane	Trichloroethylene	
Acetamide	Nickel and nickel compounds	1,3-Butadiene	**Prostate-Assoc. Carcinogens**	
Acrylamide	Nitrilotriacetic acid	Acetaldehyde	Arsenic & arsenic compounds	
Acrylonitrile	Nitrobenzene	Acrylamide	Cadmium & Cd compounds	
Arsenic and arsenic compounds	Nitromethane	Acrylonitrile	Creosote, coal tar	
Asbestos (friable)	o-Toluidine	Arsenic and arsenic compounds	Dichloromethane	
Benzene	Pentachlorophenol	Benzene	Dioxin & dioxin-like compounds	
Beryllium and beryllium compounds	Polychlorinated biphenyls	Cadmium & Cd compounds	Polycyclic aromatic compounds	
Cadmium and cadmium compounds	Polycyclic aromatic compounds	Chromium & Cr compounds	Trichloroethylene	
Carbon tetrachloride	Propylene oxide	Creosote, coal tar	**Kidney-Associated Carcinogens**	
Catechol	Propyleneimine	Dichloromethane	1,3-Butadiene	
Chlordane	Styrene	Dioxin and dioxin-like compounds	1,4-Dichlorobenzene	
Chloroform	Styrene oxide	Epichlorohydrin	Acrylamide	
Chloroprene	Tetrachloroethylene	Ethylene oxide	Arsenic and arsenic compounds	
Chromium and chromium compounds	Toluene-2,4-diisocyanate	Formaldehyde	Cadmium & Cd compounds	
Cobalt and cobalt compounds	Toluenediisocyanate	Hydrazine	Chloroform	
Creosote, coal tar	Toxaphene	Lead and lead compounds	Creosote, coal tar	
Di(2-ethylhexyl) phthalate	trans-1,3-Dichloropropene	Nickel and nickel compounds	Dichloromethane	
Di(2-ethylhexyl) phthalate	Trichloroethylene	Nitrobenzene	Dioxane	
Diaminotoluene (mixed isomers)	Urethane (Ethyl carbamate)	Polychlorinated biphenyls (PCBs)	Dioxin & dioxin-like compounds	
Dichlorobenzene (mixed isomers)	Vinyl acetate	Polycyclic aromatic compounds	Hexachlorobenzene	
Dichlorobromomethane	Vinyl bromide	Styrene	Lead and lead compounds	
Dichloromethane	Vinyl chloride	Sulfuric acid	Nickel and nickel compounds	

Table 2: Top contributors to total model scores (% of contribution to total score)

	OSHA carcinogens	Bladder carcinogens	Prostate carcinogens	Breast carcinogens	Kidney carcinogens	Lung carcinogens	NHL-associated carcinogens
Parishes	Caddo (43%)[1]	East Baton Rouge (52%)[5]	East Baton Rouge (52%)[5]	Calcasieu (28%)[7]	East Baton Rouge (29%)[9]	Caddo (69%)[11]	East Baton Rouge (36%)[13]
	St. John the Baptist (24%)[2]	Calcasieu (15%)[4]	Calcasieu (14%)[6]	East Baton Rouge (23%)[8]	Calcasieu (22%)[10]	East Baton Rouge (9%)[12]	Calcasieu (17%)[14]
Chemicals	Chromium and chromium compounds (44%)	Polycyclic aromatic compounds (84%)	Polycyclic aromatic compounds (94%)	1,3-Butadiene (23%)	1,3-Butadiene (42%)	Chromium and chromium compounds (71%)	Polycyclic aromatic compounds (35%)
	Chloroprene (24%)	Chloroform (12%)	Trichloroethylene (3%)	Benzene (23%)	Lead and lead compounds (28%)	Polycyclic aromatic compounds (7%)	1,3-Butadiene (16%)
Industries	Chemicals and allied products (71%)	Chemicals and allied products (61%)	Chemicals and allied products (57%)	Chemicals and allied products (75%)	Chemicals and allied products (48%)	Fabricated metal products (70%)	Chemicals and allied products (66%)
	Fabricated metal products (2%)	Petroleum refining and related industries (27%)	Petroleum refining and related industries (31%)	Petroleum refining and related industries (18%)	Fabricated metal products (24%)	Chemicals and allied products (17%)	Petroleum refining and related industries (25%)
Media	Fugitive air emissions (59%)	Direct water releases (53%)	Direct water releases (53%)	Fugitive air emissions (58%)	Fugitive air emissions (89%)	Fugitive air emissions (83%)	Fugitive air emissions (43%)
	Point (stack) air emissions (37%)	Fugitive air emissions (23%)	Fugitive air emissions (23%)	Point (stack) air emissions (39%)	Point (stack) air emissions (10%)	Point (stack) air emissions (12%)	Point (stack) air emissions (33%)

Figure 1: Percent of parish contribution to total statewide model score for cancer-specific carcinogens (based on 1996-2011 TRI-reported data and RSEI-generated scores).



Note: Data are displayed using the Jenks Optimization (Natural Breaks) method of classification

emissions. However, for bladder and prostate carcinogens, direct water releases were a primary contributor to total statewide model scores, and fugitive air emissions were a secondary contributor (Table 2).

DISCUSSION

According to Louisiana's Division of Administration, Louisiana "has the greatest concentration of crude oil refineries, natural gas processing plants and petrochemical facilities in the Western Hemisphere".[20] In addition, "Louisiana produces 25 percent of the nation's petrochemicals"; is the third largest producer and refiner of petroleum; and has "more than 100 major chemical plants " producing "chemicals, fertilizers and plastics, plus the feedstocks for a wide array of other products". [20] Many of the parishes identified in this investigation are consistently ranked as top contributors to the model scores (Figure 1). This is to be expected as they are among the most heavily industrialized areas of the state. With the exception of St. John the Baptist Parish, each identified parish has over 25 TRI-reporting facilities: Calcaiseu has 42 facilities (8% of the state's TRI-reporting facilities), East Baton Rouge has 40 facilities (7%), and Caddo has 26 facilities (5%), while St. John the Baptist has only 13 facilities (2%). Given the extent of industrial activities in the state, awareness of the distribution of potential hazards is essential in order to both recognize and prevent diseases associated with occupational and environmental exposures.

It is the intent of the author to motivate clinicians, especially environmental and occupational health professionals, to investigate the RSEI model for the purpose of screening their communities for potential hazards caused by industrial releases. The RSEI model allows those who want to evaluate the potential impact of TRI releases, to screen locations and facilities based on a measure which incorporates exposure and toxicity factors. The RSEI models exposure pathways for stack and fugitive air emissions, direct surface water releases, transfers to publically owned treatment works, off site transfers and on-site land releases; and calculates risk-related results for air and surface water pathways.[15] The models, parameters, algorithms and assumptions used to estimate exposure are too lengthy to list here, but are described in detail in EPA's technical documentation.[15] As with all models, results are based on simplified inputs, such as those measuring toxicity, environmental fate and transport, and potential exposure. Air pathways were modeled using the American Meteorological Society/EPA Regulatory Model (AERMOD)- a steady state Gaussian plume model used to estimate pollutant concentrations downwind of a stack or area source. Facility-specific parameters, meteorology and chemical-specific first order decay rates are used. Surface water pathways are modeled by estimating contaminant concentrations in drinking water and fish, where a public water system's intake is located in a stream path of the release. Some data used in surface water models include EPA's records of discharge permits, decay coefficients, estimates of water velocity, public water system distribution details from EPA's Safe Drinking Water Information System and chemical-specific bioconcentration factors. [15] The sources for exposure factors, toxicity weights and demographics are the EPA's Exposure Factors Handbook,[21] EPA's Integrated Risk Information System,[17] and the US Census data, respectively. As stated in EPA's RSEI methodology document, [15] "The exposure algorithms are intended to be simple ways to gauge relative risks from releases to different media in a consistent, defensible way, by modeling and estimating exposure. In some cases, the modeling is purposely simplified, given the lack of site-specific data". In short, the RSEI is a free and simple to use model that can assist clinicians in local investigations, when the causal factor of a disease is unknown, or when environmental exposure factors are suspected.

Results presented are subject to several limitations due to the availability and quality of model inputs and model assumptions. For example, not all sources of carcinogens are included in this analysis- mobile sources and industries under the reporting threshold are not represented; and some carcinogens are not reported to the TRI Program. Also, model scores could not be generated for chemicals lacking information required for modeling, such as measures of toxicity. Probably the greatest limitation is that industry-reported TRI data are hard to verify and may be prone to biased reporting. One cannot exclude the possibility that industries under-report actual releases to meet regulatory requirements. Results should also be put into the proper context. That is, this analysis does not consider chemicals that people are exposed to on a more common basis. Toxicants can be found in vehicle exhaust, processed food, air fresheners, pesticides, paints and varnishes, and cleaning products, just to name a few sources. It is estimated that the average American spends 90 percent of their time indoors. Indoor pollutant levels may be two to five times higher than outdoor pollutant levels.[22] Thus, the RSEI model is most suitable for use by environmental and occupational clinicians to identify and screen potential hazards to workers and members of fenceline communities.

CONCLUSIONS

Caddo, St. John the Baptist, East Baton Rouge and Calcasieu parishes were consistently ranked as the highest contributors to cancer-specific model scores. Clinicians should be cognizant of industrial hazards in their communities, and conduct environmental and occupational histories of patients in fenceline communities or in industrial occupations. The RSEI model is an easy to use method for screening potential industry-related hazards at the parish or neighborhood level; and is relevant to doctors serving industry workers and fenceline communities. It is intended that the results presented here will guide and influence state monitoring efforts, regulatory oversight, health

investigations, and clinician awareness.

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Prioritization of Louisiana Parishes based on Industrial Releases of Known or Suspected Carcinogens

Adrienne Katner, MS, DEnv

This investigation evaluated the geographic distribution of carcinogen releases by Louisiana industries to prioritize areas for regulatory oversight, research and monitoring, and to promote clinician awareness and vigilance. Data on estimated industry releases for the period between 1996 and 2011 were obtained from the US Environmental Protection Agency's Toxics Release Inventory. Chemicals associated with cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were identified. The Risk Screening Environmental Indicators model was used to derive measures or model scores based on chemical toxicity, fate and transport, and population characteristics. Parishes, chemicals, industries and media generating the highest model scores were identified. Parishes with the highest model scores were East Baton Rouge, Calcasieu, Caddo and St. John the Baptist. Clinicians should carefully monitor cancer cases in these areas, and if patients reside near or work in industry, an occupational and environmental history should be considered.

INTRODUCTION

In Louisiana, cancer incidence is significantly higher than the national rate for white men, black men and black women; and cancer mortality is significantly higher for blacks and whites of both sexes.[1] The reasons for these disparities are not fully understood,[1] but may include factors such as genetic predisposition, behavioral influences like smoking, access to medical care or early screening, and environmental hazard exposures. Environmental and occupational exposures have been estimated to contribute to only 6 percent of all cancer deaths in the US.[2] However, an accurate measure of the contribution of these factors to cancer risk is impossible, as the causes of cancer can be difficult to identify and may be multifactorial.[3-5] While there is little doubt that lifestyle factors such as smoking, physical inactivity, poor nutrition and obesity are the most important contributors to cancer when compared to environmental or occupational exposures, lower income workers and communities may have disproportionately higher exposures to occupational and environmental carcinogens.[6] Therefore, clinicians should be aware of the types of industrial hazards that may be present in their communities.

Most industries have been required to report toxic environmental releases to the US Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI) Program since 1988. These facilities include those that meet the following conditions: 1) employ 10 or more full time workers; and 2) are in a specific industrial sector or are a federal facility; and 3) manufacture or process more than 25,000 pounds of a listed chemical or uses more than 10,000 pounds of a listed chemical in a given year.[7] Over 682 chemicals and chemical categories must be reported along with information describing the facility, the chemical released, the release amount and the media of release.[7] TRI data on chemical releases have proved useful to public health surveillance and research activities.[8-9] For example, areas with higher levels of TRI releases are significantly associated with higher mortality rates.[8] Areas with higher levels of TRI-reported carcinogen releases are associated with significantly higher hospitalization rates.[9] And a significantly increased risk of lung cancer incidence has been associated with TRI releases of chromium, formaldehyde and nickel.[10] Studies of this kind have been useful in generating hypotheses and stimulating research, but like all ecological studies, they are prone ecological fallacy. They merely demonstrate association, not causation, because of unmeasured and uncontrolled confounding factors.

Several studies have used TRI data to identify areas and populations facing the highest potential health risks from industrial releases.[11-13] Most previous studies have relied on quantity-based evaluations, but did not account for factors such as chemical toxicity, environmental fate and transport, or population proximity and characteristics. In 2004, Chakraborty[11] was one of the first researchers to incorporate Toxic Equivalency Potentials, a crude measure of potential harm based on toxicity and environmental fate, into a TRI-based screening study to identify states facing

the highest potential carcinogenic and non-carcinogenic risk from industrial toxic releases. And in 2010, Lim *et al*[12] coupled TRI data with toxicity potentials to rank and prioritize chemicals, states and industries. Both of these nationwide studies identified Louisiana as one of the ten states with the highest potential cancer impact from TRI releases.

This investigation extends those two prior studies but narrows the focus to Louisiana parishes and bases the screening on a novel measure. The US EPA's Risk Screening Environmental Indicators (RSEI) model is used to derive chemical- and facility-specific scores. The RSEI model estimates a surrogate "dose" based on chemical-specific reported release quantities, pathway-specific modeling of the chemical fate and transport through the environment, and facility-specific population characteristics and exposure factors.[14-15] It then incorporates toxicity information to calculate a relative "risk" score for the entire population.[15] The RSEI-based score is not a true risk estimation- it is a unitless measure and is not independently meaningful. Rather, it is a relative measure that can be compared to other RSEI-based scores to compare and prioritize areas, chemicals and industries.[14] In this study, model scores were generated for groups of chemicals with known or suspected associations to specific cancers. Cancers of the prostate, lung, bladder, kidney, breast and non-Hodgkin lymphoma were selected on the basis of their high state incidence rates[1] and their association with environmental hazards in the literature. These cancer-specific scores were then used to prioritize parishes and industries. Rankings are intended to serve as a guide to direct local research or monitoring investigations, and promote clinician awareness and vigilance. It should be emphasized that the information provided here is for screening purposes only and must not be construed to imply any causal relationship between a release and an individual case of disease. Cancer incidence rates were not purposefully included to prevent unintended linkages with these derived scores, as that is not the objective of this analysis. Cancer incidence rates can be obtained from the Louisiana Tumor Registry's website.[1] The results highlighted serve only as a starting point for drawing attention to areas that have the potential for health impact due to industrial toxic releases.

MATERIALS AND METHODS

Environmental releases of carcinogens reported to the TRI Program between 1996 and 2011 were evaluated. Occupational Safety and Health Administration (OSHA) carcinogens and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and with non-Hodgkin lymphoma (NHL) were the focus of this investigation. Several sources were used to create a list of chemicals considered to be known or suspected carcinogens. These included the International Agency for Research on Cancer (IARC),[16] the EPA's Integrated Risk Screening Information System (IRIS),[17] the National Toxicology Program's 12th Report on Carcinogens,[18] and the OSHA Select Carcinogen list.[19] Table 1 presents the list of chemicals evaluated.

Technical information about the methodology and assumptions used in the RSEI model for calculating relative scores for releases and transfers to air and water are available online.[14] Release estimates (pounds), which are values directly reported to the TRI program based on facility calculations, were also obtained using the RSEI model. The sum of releases and model scores were derived for cancer-specific carcinogens by chemical, medium of release (only air and water releases were evaluated), industry (based on 2-digit primary standard industrial classification or code or SIC) and parish. Aggregate releases and model scores were then ranked to prioritize chemicals, media, industries and parishes.

RESULTS

Model scores were used to prioritize parishes releasing OSHA carcinogens, and carcinogens associated with cancers of the prostate, lung, bladder, kidney and breast, and non-Hodgkins lymphoma (NHL) (Table 2). Figure 1 presents the percent of parish contribution to the total state model score for cancer-specific carcinogens. Parishes consistently ranked as the highest contributors to statewide model scores included: Caddo, St. John the Baptist, East Baton Rouge and Calcasieu. These parishes were also along the highest contributors to statewide model scores for OSHA carcinogens.

Carcinogens contributing the greatest amounts to the total statewide cancer-specific model scores included: chromium, polycyclic aromatic compounds and 1,3-butadiene. Other high carcinogen contributors to the total model scores included: chloroprene, chloroform, trichloroethylene, benzene, and lead and lead compounds (Table 2). Many of these chemicals with the largest model scores were not among those with the largest releases (data not shown), highlighting the impact that other factors, such as chemical fate and transport, play in the potential for exposure and health impact.

Industries contributing the greatest amounts to the total statewide cancer-specific model scores included: chemicals and allied products, fabricated metal products, and petroleum refining and related industries (Table 2). In Calcasieu Parish, 99% of TRI-reporting facilities are industries within the categories of chemicals and allied products or petroleum refining and related industries. These industries also account for 99.6% of TRI-reporting facilities in East Baton Rouge Parish. In Caddo Parish, 'fabricated metal products' comprise about 99.5% of TRI-reporting facilities; and in St. John the Baptist Parish, 'chemicals and allied products' comprise about 99.6% of TRI-reporting facilities.

The media of release contributing the greatest to the total statewide model scores for most cancer-specific carcinogen groups were fugitive air emissions and point (or stack) air

Table 1: List of cancer-specific carcinogens reported to the EPA's TRI Program and included in the evaluation

OSHA Carcinogens	OSHA Carcinogens (continued)	Breast-Associated Carcinogens	NHL-Associated Carcinogens	Kidney-Associated Carcinogens (continued)
1,1-Dimethyl Hydrazine	Diethyl sulfate	1,2-Dichloroethane	1,2-Dichloroethane	Tetrachloroethylene
1,2,3-Trichloropropane	Dimethyl sulfate	1,3-Butadiene	1,3-Butadiene	Trichloroethylene
1,2-Butylene oxide	Dioxane	Acetaldehyde	Acetaldehyde	**Bladder-Associated Carcinogens**
1,2-Dibromoethane	Dioxin and dioxin-like compounds	Benzene	Arsenic & arsenic compounds	Arsenic and arsenic compounds
1,2-Dichloroethane	Epichlorohydrin	Carbon tetrachloride	Benzene	Cadmium & Cd compounds
1,3-Butadiene	Ethyl acrylate	Dichloromethane	Cadmium & Cd compounds	Cadmium & Cd compounds
1,3-Dichloropropylene	Ethylbenzene	Dioxane	Carbon tetrachloride	Chloroform
2,4-Diaminotoluene	Ethylene oxide	Hydrazine	Formaldehyde	Creosote, coal tar
2,4-Dinitrotoluene	Formaldehyde	Nitrobenzene	Hexachlorobenzene	Dichlorobromomethane
2,6-Xylidine	Glycidol	Polychlorinated biphenyls (PCBs)	Lead and lead compounds	Lead and lead compounds
2-Nitropropane	Heptachlor	Propyleneimine	Polychlorinated biphenyl (PCBs)	Polycyclic aromatic compounds
4,4'-Methylenedianiline	Hexachlorobenzene	Styrene	Polycyclic aromatic compounds	Tetrachloroethylene
4-Aminoazobenzene	Hexachloroethane	Toluenediisocyanate	Styrene	
4-Aminodiphenyl	Lead and lead compounds	**Lung-Associated Carcinogens**	Tetrachloroethylene	
Acetaldehyde	Naphthalene	1,2-Dichloroethane	Trichloroethylene	
Acetamide	Nickel and nickel compounds	1,3-Butadiene	**Prostate-Assoc. Carcinogens**	
Acrylamide	Nitrilotriacetic acid	Acetaldehyde	Arsenic & arsenic compounds	
Acrylonitrile	Nitrobenzene	Acrylamide	Cadmium & Cd compounds	
Arsenic and arsenic compounds	Nitromethane	Acrylonitrile	Creosote, coal tar	
Asbestos (friable)	o-Toluidine	Arsenic and arsenic compounds	Dichloromethane	
Benzene	Pentachlorophenol	Benzene	Dioxin & dioxin-like compounds	
Beryllium and beryllium compounds	Polychlorinated biphenyls	Cadmium & Cd compounds	Polycyclic aromatic compounds	
Cadmium and cadmium compounds	Polycyclic aromatic compounds	Chromium & Cr compounds	Trichloroethylene	
Carbon tetrachloride	Propylene oxide	Creosote, coal tar	**Kidney-Associated Carcinogens**	
Catechol	Propyleneimine	Dichloromethane	1,3-Butadiene	
Chlordane	Styrene	Dioxin and dioxin-like compounds	1,4-Dichlorobenzene	
Chloroform	Styrene oxide	Epichlorohydrin	Acrylamide	
Chloroprene	Tetrachloroethylene	Ethylene oxide	Arsenic and arsenic compounds	
Chromium and chromium compounds	Toluene-2,4-diisocyanate	Formaldehyde	Cadmium & Cd compounds	
Cobalt and cobalt compounds	Toluenediisocyanate	Hydrazine	Chloroform	
Creosote, coal tar	Toxaphene	Lead and lead compounds	Creosote, coal tar	
Di(2-ethylhexyl) phthalate	trans-1,3-Dichloropropene	Nickel and nickel compounds	Dichloromethane	
Di(2-ethylhexyl) phthalate	Trichloroethylene	Nitrobenzene	Dioxane	
Diaminotoluene (mixed isomers)	Urethane (Ethyl carbamate)	Polychlorinated biphenyls (PCBs)	Dioxin & dioxin-like compounds	
Dichlorobenzene (mixed isomers)	Vinyl acetate	Polycyclic aromatic compounds	Hexachlorobenzene	
Dichlorobromomethane	Vinyl bromide	Styrene	Lead and lead compounds	
Dichloromethane	Vinyl chloride	Sulfuric acid	Nickel and nickel compounds	

Table 2: Top contributors to total model scores (% of contribution to total score)

	OSHA carcinogens	Bladder carcinogens	Prostate carcinogens	Breast carcinogens	Kidney carcinogens	Lung carcinogens	NHL-associated carcinogens
Parishes	Caddo (43%)[1]	East Baton Rouge (52%)[5]	East Baton Rouge (52%)[5]	Calcasieu (28%)[7]	East Baton Rouge (29%)[9]	Caddo (69%)[11]	East Baton Rouge (36%)[13]
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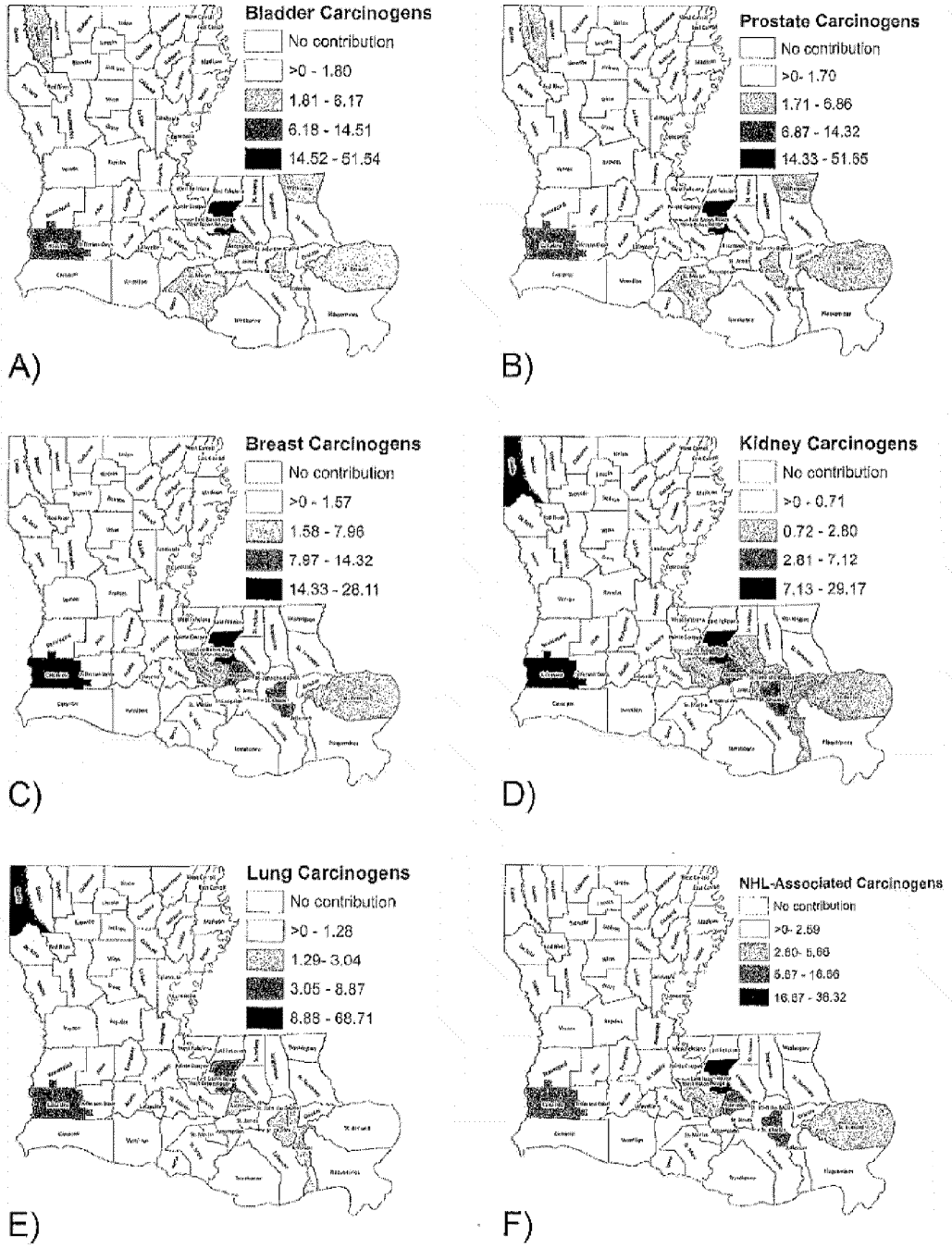
Chemicals	Chromium and chromium compounds (44%)	Polycyclic aromatic compounds (84%)	Polycyclic aromatic compounds (94%)	1,3-Butadiene (23%)	1,3-Butadiene (42%)	Chromium and chromium compounds (71%)	Polycyclic aromatic compounds (35%)
	Chloroprene (24%)	Chloroform (12%)	Trichloroethylene (3%)	Benzene (23%)	Lead and lead compounds (28%)	Polycyclic aromatic compounds (7%)	1,3-Butadiene (16%)
Industries	Chemicals and allied products (71%)	Chemicals and allied products (61%)	Chemicals and allied products (57%)	Chemicals and allied products (75%)	Chemicals and allied products (48%)	Fabricated metal products (70%)	Chemicals and allied products (66%)
	Fabricated metal products (2%)	Petroleum refining and related industries (27%)	Petroleum refining and related industries (31%)	Petroleum refining and related industries (18%)	Fabricated metal products (24%)	Chemicals and allied products (17%)	Petroleum refining and related industries (25%)
Media	Fugitive air emissions (59%)	Direct water releases (53%)	Direct water releases (53%)	Fugitive air emissions (58%)	Fugitive air emissions (89%)	Fugitive air emissions (83%)	Fugitive air emissions (43%)
	Point (stack) air emissions (37%)	Fugitive air emissions (23%)	Fugitive air emissions (23%)	Point (stack) air emissions (39%)	Point (stack) air emissions (10%)	Point (stack) air emissions (12%)	Point (stack) air emissions (33%)

Figure 1: Percent of parish contribution to total statewide model score for cancer-specific carcinogens (based on 1996-2011 TRI-reported data and RSEI-generated scores).



Note: Data are displayed using the Jenks Optimization (Natural Breaks) method of classification

emissions. However, for bladder and prostate carcinogens, direct water releases were a primary contributor to total statewide model scores, and fugitive air emissions were a secondary contributor (Table 2).

DISCUSSION

According to Louisiana's Division of Administration, Louisiana "has the greatest concentration of crude oil refineries, natural gas processing plants and petrochemical facilities in the Western Hemisphere".[20] In addition, "Louisiana produces 25 percent of the nation's petrochemicals"; is the third largest producer and refiner of petroleum; and has "more than 100 major chemical plants " producing "chemicals, fertilizers and plastics, plus the feedstocks for a wide array of other products". [20] Many of the parishes identified in this investigation are consistently ranked as top contributors to the model scores (Figure 1). This is to be expected as they are among the most heavily industrialized areas of the state. With the exception of St. John the Baptist Parish, each identified parish has over 25 TRI-reporting facilities: Calcaiseu has 42 facilities (8% of the state's TRI-reporting facilities), East Baton Rouge has 40 facilities (7%), and Caddo has 26 facilities (5%), while St. John the Baptist has only 13 facilities (2%). Given the extent of industrial activities in the state, awareness of the distribution of potential hazards is essential in order to both recognize and prevent diseases associated with occupational and environmental exposures.

It is the intent of the author to motivate clinicians, especially environmental and occupational health professionals, to investigate the RSEI model for the purpose of screening their communities for potential hazards caused by industrial releases. The RSEI model allows those who want to evaluate the potential impact of TRI releases, to screen locations and facilities based on a measure which incorporates exposure and toxicity factors. The RSEI models exposure pathways for stack and fugitive air emissions, direct surface water releases, transfers to publically owned treatment works, off site transfers and on-site land releases; and calculates risk-related results for air and surface water pathways.[15] The models, parameters, algorithms and assumptions used to estimate exposure are too lengthy to list here, but are described in detail in EPA's technical documentation.[15] As with all models, results are based on simplified inputs, such as those measuring toxicity, environmental fate and transport, and potential exposure. Air pathways were modeled using the American Meteorological Society/EPA Regulatory Model (AERMOD)- a steady state Gaussian plume model used to estimate pollutant concentrations downwind of a stack or area source. Facility-specific parameters, meteorology and chemical-specific first order decay rates are used. Surface water pathways are modeled by estimating contaminant concentrations in drinking water and fish, where a public water system's intake is located in a stream path of the release. Some data used in surface water models include EPA's records of discharge permits, decay coefficients, estimates of water velocity, public water system distribution details from EPA's Safe Drinking Water Information System and chemical-specific bioconcentration factors. [15] The sources for exposure factors, toxicity weights and demographics are the EPA's Exposure Factors Handbook,[21] EPA's Integrated Risk Information System,[17] and the US Census data, respectively. As stated in EPA's RSEI methodology document, [15] "The exposure algorithms are intended to be simple ways to gauge relative risks from releases to different media in a consistent, defensible way, by modeling and estimating exposure. In some cases, the modeling is purposely simplified, given the lack of site-specific data". In short, the RSEI is a free and simple to use model that can assist clinicians in local investigations, when the causal factor of a disease is unknown, or when environmental exposure factors are suspected.

Results presented are subject to several limitations due to the availability and quality of model inputs and model assumptions. For example, not all sources of carcinogens are included in this analysis- mobile sources and industries under the reporting threshold are not represented; and some carcinogens are not reported to the TRI Program. Also, model scores could not be generated for chemicals lacking information required for modeling, such as measures of toxicity. Probably the greatest limitation is that industry-reported TRI data are hard to verify and may be prone to biased reporting. One cannot exclude the possibility that industries under-report actual releases to meet regulatory requirements. Results should also be put into the proper context. That is, this analysis does not consider chemicals that people are exposed to on a more common basis. Toxicants can be found in vehicle exhaust, processed food, air fresheners, pesticides, paints and varnishes, and cleaning products, just to name a few sources. It is estimated that the average American spends 90 percent of their time indoors. Indoor pollutant levels may be two to five times higher than outdoor pollutant levels.[22] Thus, the RSEI model is most suitable for use by environmental and occupational clinicians to identify and screen potential hazards to workers and members of fenceline communities.

CONCLUSIONS

Caddo, St. John the Baptist, East Baton Rouge and Calcasieu parishes were consistently ranked as the highest contributors to cancer-specific model scores. Clinicians should be cognizant of industrial hazards in their communities, and conduct environmental and occupational histories of patients in fenceline communities or in industrial occupations. The RSEI model is an easy to use method for screening potential industry-related hazards at the parish or neighborhood level; and is relevant to doctors serving industry workers and fenceline communities. It is intended that the results presented here will guide and influence state monitoring efforts, regulatory oversight, health

investigations, and clinician awareness.

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A constrained maximum likelihood approach to evaluate the impact of dose metric on cancer risk assessment: Application to b-chloroprene

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abstract

b-Chloroprene (2-chloro-1,3-butadiene, CD) is used in the manufacture of polychloroprene rubber. Chronic inhalation studies have demonstrated that CD is carcinogenic in B6C3F1 mice and Fischer 344 rats. However, epidemiological studies do not provide compelling evidence for an increased risk of mortality from total cancers of the lung. Differences between the responses observed in animals and humans may be related to differences in toxicokinetics, the metabolism and detoxification of potentially active metabolites, as well as species differences in sensitivity. The purpose of this study was to develop and apply a novel method that combines the results from available physiologically based kinetic (PBK) models for chloroprene with a statistical maximum likelihood approach to test commonality of low-dose risk across species. This method allows for the combined evaluation of human and animal cancer study results to evaluate the difference between predicted risks using both external and internal dose metrics. The method applied to mouse and human CD data supports the hypothesis that a PBK-based metric reconciles the differences in mouse and human low-dose risk estimates and further suggests that, after PBK metric exposure adjustment, humans are equally or less sensitive than mice to low levels of CD exposure.

1. Introduction

b-Chloroprene (CD, CAS# 126-99-8, 2-chloro-1,3-butadiene) is a compound used in the manufacture of polychloroprene rubber. Chronic inhalation studies in animals have demonstrated that CD is carcinogenic in B6C3F1 mice and Fischer 344 rats in multiple target organs (lung, liver, circulatory systems, forestomach, Harderian gland, kidney, mammary gland, mesentery, oral cavity, skin, and thyroid gland) (Melnick et al., 1999; National Toxicology Program, 1998). In addition, respiratory and liver cancers have been associated with CD exposure in several epidemiological studies (Acquavella and Leonard, 2001); however, interpretation of these findings has been difficult due to methodological limitations, including the inability to assign quantitative values for CD exposures, the small number of observed outcomes, and the small sample sizes for occupational studies (Marsh et al., 2007a). This makes the comparison of estimates of risk based on animal versus human results difficult.

While epidemiological studies are available for chloroprene, due to the uncertainties in the epidemiological studies the most recent quantitative risk assessment conducted by the USEPA (2010) used only animal data. The resulting cancer unit risk is driven by the most sensitive endpoint in animals, the incidence of lung tumors in female mice. Integration of the epidemiological studies does not provide compelling evidence for an increased risk of mortality from total cancers of the lung following inhalation exposure to chloroprene (Marsh et al., 2007a,b).

Previous studies have examined differences in toxicokinetics between animals and humans to determine if this is potentially

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the contributing factor to the differences in response between animals and humans. The initial step in metabolism is oxidation forming a stable epoxide, (1-chloroethenyl) oxirane, a genotoxicant that might be involved in the observed carcinogenicity in animals (Himmelstein et al., 2004b). Differences between the responses observed in animals and humans may be related to differences in toxicokinetics, to the metabolism and detoxification of potentially active metabolites (Himmelstein et al., 2004a,b), as well as to differences in species sensitivity. Specifically, Himmelstein et al. (2004a) found that the oxidation (Vmax/Km) of CD in liver was slightly faster in rats and mice than in humans and hamsters, and in lung microsomes was much greater for mice compared to other species. In addition, hydrolysis (Vmax/Km) of (1-chloroethenyl) oxirane, in liver and lung microsomes, was faster for humans and hamsters than for rats and mice.

In current risk assessments for chloroprene (USEPA, 2010), external exposure estimates are relied upon, which does not consider species differences in toxicokinetics. These differences may be critical in characterizing the potential risk of cancer following exposure to chloroprene, especially if the generation of a metabolite is related to the potential for cancer risk. The availability of physiologically based kinetic (PBK) models for both mice and humans (Yang et al., 2012) provides a unique opportunity for comparison of animal and human risk estimates based on external and internal exposure metrics. The PBK model for chloroprene incorporates the available data regarding species differences in metabolism of chloroprene. Application of the model allows for species-specific estimation of internal exposure metric, specifically the amount of chloroprene metabolized per gram of lung tissue. Risk estimates can then be compared across species based on this equivalent internal exposure metrics rather than external air concentrations.

The purpose of this study was to develop and apply a novel method that combines the results from available PBK models for chloroprene with a statistical maximum likelihood approach to test commonality of low-dose risk across species. This method allows for the combination of human and animal cancer study results to evaluate the difference between risk estimates obtained using both external and internal dose metrics.

The maximum likelihood approach applied allows for the evaluation of the ability of traditional dose–response models, such as the Multistage model, to describe the response pattern under the constraint of equal risk at a dose of interest (either internal or external), specifically a possible point of departure (POD). The results provide a demonstration of which dose metric provides statistically equivalent human- and animal-based risk estimates. Additional analyses were also conducted to investigate the impact of uncertainty in the estimated exposure levels for the human occupational study and to address the question of potential cross-species pharmacodynamic differences.

2. Material and methods

The method described here requires both animal data (a well-conducted two-year bioassay) and epidemiological data sufficient to allow dose-response analysis. Rather than modeling them separately, the approach adopted is to jointly model the selected studies to determine if, and under what circumstances, risk estimates of interest can be determined to be consistent across species. Jointly modeling the data requires software that allows for constrained maximization of the combined likelihood of the animal and human dose–response relationships with testing of hypotheses based on the comparison of the constrained maximum likelihood to the unconstrained (separate) likelihoods for the two species. Fig. 1 depicts the overall procedure.

2.1. Animal data

A two-year inhalation study of CD was conducted in F344/N rats and B6C3F$_1$ mice (National Toxicology Program, 1998). This is the bioassay relied upon by the Environmental Protection Agency (EPA) in the recent CD Integrated Risk Information System (IRIS) assessment (USEPA, 2010). Groups of 50 males and 50 females were exposed by inhalation for 6 h per day 5 days per week for 2 years to 0, 12.8, 32 or 80 ppm of CD. The National Toxicology Program (NTP) (1998) concluded that there was clear evidence of carcinogenicity in both the rats and mice following inhalation exposure to CD. In the F344/N rats, this conclusion was based on the increased incidences of neoplasms of the thyroid gland and kidney in males and females, increased incidences of neoplasms in the lung in males only and in the oral cavity and mammary gland in females only. In the B6C3F$_1$ mice, the conclusion of clear evidence of carcinogenicity was based on the increased incidence of neoplasms in the lung, circulatory system, forestomach and Harderian gland in both sexes, in the kidney for males only and the mammary gland, liver and skin for females only (see Table 5-4 in USEPA, 2010).

Based on the NTP (1998) results, USEPA (2010) concluded that that mouse is the most sensitive species, due to the increased tumor incidence and multisite distribution in the mouse relative to the rat. The EPA calculated a composite unit risk from all the female mice cancer endpoints listed above (9.8×10^{-1} per ppm; 2.7×10^{-4} per $\mu g/m^3$), and the unit risk estimated from the combined incidence of lung adenomas or carcinomas in the female mice produced the highest site-specific unit risk (6.4×10^{-1} per ppm; 1.8×10^{-4} per $\mu g/m^3$). As it was the most sensitive of the site-specific endpoints, combined lung adenomas and carcinomas is the endpoint considered in the current analysis. Analyses of rat responses, and perhaps additional mouse responses, may follow, given the success of this investigation.

2.2. Human data

Marsh et al. (2007a,b) conducted a historical cohort study to investigate the mortality of industrial workers potentially exposed to CD and other substances (including a potential confounding co-exposure to vinyl chloride). This study represents one of the most recent epidemiological studies and the design attempted to address the problems identified with earlier studies by conducting a detailed exposure assessment for both chloroprene and vinyl chloride monomer. The emphasis of the study was on cancer mortality, including respiratory system cancer. Four different CD production sites (i.e., Louisville, KY; Pontchartrain, LA; Maydown, Northern Ireland; and Grenoble, France) were included in the Marsh et al. study. The Louisville cohort examined by Marsh et al. (2007a,b) had the greatest number of exposed individuals, the greatest number of person-years of follow-up, and the greatest average exposure level (both in terms of the intensity level, ppm, and in terms of cumulative exposure, ppm-years). The greater exposure levels, combined with the greatest number of exposed individuals, increase the probability of detecting any carcinogenic effect following exposure to CD. Respiratory system cancer mortality from the Louisville cohort was used in this analysis as those data came from the best epidemiological dataset available (in terms of adequacy of size and suitability for dose–response analysis) that measured an endpoint that was comparable to the most sensitive endpoint in mice. The other cohorts may be subject to future analyses; inclusion of additional cohorts may increase the power of the epidemiological modeling.

For the Louisville cohort, approximate quartiles of the data were determined by Marsh et al. (2007b) based on the distribution of death from all cancers, and these quartiles were used to define

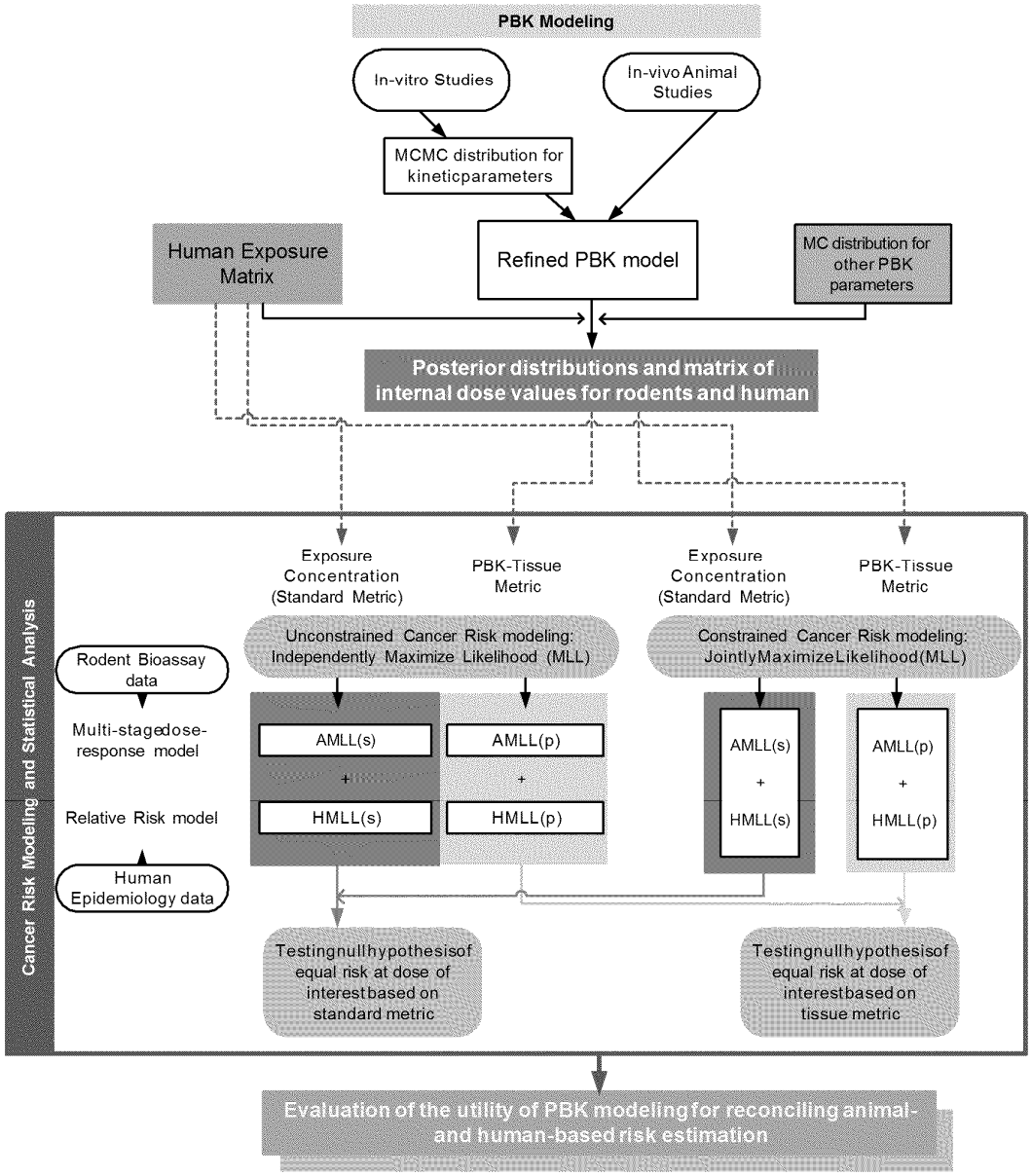

Fig. 1. Overview of physiological based kinetic modeling probabilistic dose response modeling.

the subgroups for all other cancer types, including the respiratory cancer used in this analysis. The exposure reconstruction detailed in Esmen et al. (2007b) was used, in combination with the Occupational Cohort Mortality Analysis Program (OCMAP) (described in detail in Marsh et al., 1998) to determine the quartile-specific and overall average cumulative exposure.

2.3. Estimation of exposure/dose

In the evaluation of the animal data, external air concentrations used in the exposure-response modeling were the administered air concentrations in the NTP (1998) study in ppm adjusted to an equivalent continuous exposure, adjusting for hours per day (6/24) and days per week (5/7) (Table 1). Similarly, the human cumulative doses were adjusted from occupational to continuous exposure by adjusting for the number of work weeks per year (50/52), for work days per week (5/7) and for percentage of total daily inhalation that occurs during work hours (10/20) (USEPA, 2009). Adjusted values are shown in Table 2.

Based on the range of reported exposures for each quartile, the midpoints of cumulative exposure for the first three exposure groups were used (assumed to characterize the respective group average exposure for dose–response modeling). However, because the high exposure group was characterized as 164.053+ ppm-years with no highest exposure value, an approach was needed to characterize the average exposure for this group (Table 2). The average exposure used for the highest group was calculated based on the midpoint values for exposure groups 1 through 3, the overall average cumulative exposure computed by OCMAP, and the number of person-years apportioned to each group, shown here:

Table 1
Animal data modeled via the multistage model.

Dose group	Continuous exposure equivalent (ppm)	PBK metric (lmole/g-lung/day)	Group size	Number of animals with respiratory system cancer
1	0	0	50	4
2	2.3	0.705	49	28
3	5.7	1.12	50	34
4	14.3	1.47	50	42

Table 2
Human data modeled via a linear relative risk model.

Cumulative exposure group	Published cumulative exposure ranges (ppm-years)	Average cumulative exposure (ppm-years)	Assumed adjusted average cumulative exposure (ppm-years)	PBK metric (lmole of metabolite/g lung/day-years)	Person years of observation	Deaths from respiratory system cancer	SMR	Computed expected
1	<4.747	2.37	0.814	0.0083	68918	62	0.71	87.32
2	4.747–55.918	30.3	10.4	0.107	56737	67	0.71	94.37
3	55.918–164.052	110	37.8	0.387	39840	77	0.92	83.70
4	164.053+	297[a]	102	1.05	32424	60	0.65	92.31

[a] Calculated using text Eq. (1).

$$\text{ppm-years}(\text{avg},\text{total}) = \sum_{i} \text{ppm-years}(\text{avg},i) \cdot \text{PY}(i) / \text{PY}(\text{total}) \quad (1)$$

where ppm-years(avg, total) is the average cumulative exposure for the entire cohort (80.35 ppm-years), ppm-years(avg, i) is the assumed average cumulative exposure for groups 1-3 or the unknown X ppm-years for group 4; PY(total) is the total number of person years of follow-up for the cohort (197919); and PY(i) is the person years of follow-up for group i (68918, 56737, 39840, and 32424 years for groups 1 through 4, respectively). The values for the ppm-year ranges and person years of follow-up (see also Table 2) are from Marsh et al. (2007b). The only unknown in the equation above, X, is for the ppm-years for group 4. Solving for X gives an estimate of the cumulative exposure for group 4 of 297 ppm-years.[1]

An internal dose metric (PBK metric) was estimated for both the animal and human datasets using the PBK model by Yang et al. (2012). Following Markov Chain Monte Carlo (MCMC) analyses, Yang et al. derived a set of posterior distributions for each of the kinetic parameters in both the mouse and the human PBK models. The mean from each distribution (i.e., one for each kinetic parameter) as well as the standard physiological and partition coefficient values (Yang et al., 2012) for each species were used in the corresponding PBK model to derive the internal dose metric of lmoles of metabolized CD/g lung/day for each exposure group in both the mouse experimental study and the human occupational study. Such a metric reflects the estimated metabolism of CD to reactive metabolites, including (1-chloroethenyl) oxirane, which are the proposed carcinogenic moieties (Yang et al., 2012). Since metabolism of CD is different between mice and humans, the use of PBK model estimates of internal dose, as a measure of exposure, provides a method to account for these species-specific differences.

For both the mouse and the human, the models were run for a week-long exposure (5 days per week). It was observed that after the 2 (weekend) days of non-exposure, chloroprene was cleared from the body for both species. Thus, a single week of modeling the experimental exposures or occupational exposures was sufficient to calculate the lifetime daily average.

2.4. Calculation of animal-based risks

For the current assessment, the Multistage model provided in the USEPA Benchmark Dose Software (BMDS) program (USEPA, 2012) was fit to the female mice lung adenoma or carcinoma incidence data using the continuous exposure equivalent in ppm (adjusted from 6 h per day 5 days per week to continuous). In addition, the model was also fit to the data using the internal PBK metric of lmole CD metabolized/g of lung/day obtained from simulations of the Yang et al. (2012) PBK model (Table 1).

The multistage model has the mathematical form:

$$P(d) = 1 - e^{-(q_0 + q_1 d + \ldots + q_k d^k)} \quad (2)$$

where d is the average lifetime daily dose, P(d) is the lifetime probability of tumor from the dose level d, and $q_0, \ldots, q_k$ are nonnegative parameters estimated by fitting the model to experimental animal data. The multistage modeling performed in this analysis assumed k = 2, i.e., it used a two-stage model.

The multistage model is a flexible statistical model that can describe both linear and non-linear dose-response patterns. It has been used as the standard for cancer risk analysis, and for many years the default dose-response model for federal and state regulatory agencies in the United States for calculating quantitative estimates of low-dose carcinogenic risks from animal data (USEPA, 1986, 2005).

The choice of a low-dose extrapolation method used by the EPA, in particular, in dose–response assessments should be informed by the available information on the mode of action of cancer, as well as other relevant biological information, and not solely on goodness-of-fit to the observed tumor data (USEPA, 1992). However, when data are limited or when uncertainty exists regarding the mode of action, models which incorporate low-dose linearity are the default approach. EPA usually employs the linearized multistage procedure in the absence of adequate information to the contrary; many of the available IRIS values are based on the results from this model. In that capacity, it is regularly used on data sets with only a few data points as is common for animal studies.

Using the external and internal dose metrics for CD, a single maximized log-likelihood was determined for each: the

[1] This approach used to determine the average concentration for the highest exposure group was deemed preferable to using a midpoint between 164 ppm-years and 1351.5 ppm-years, the reported maximum seen in the cohort. The dose for the highest group would have been larger (758 ppm-years) and would not have maintained the reported average ppm-year value for the entire cohort. Rather than relying upon a midpoint of the range of exposure, the consideration of average values for grouped exposure summaries in the current approach reflects all of the available information regarding cohort exposure.

unconstrained animal maximum log-likelihood for the standard (or external) metric (AMLLs) and the unconstrained maximized log-likelihood for the internal metric (AMLLp) (Fig. 1). Each of the AMLLx values represents the usual data-specific measure of the fit of the model to the animal bioassay results and is the maximum value of that log-likelihood with no other constraints.

2.5. Calculation of epidemiology-based risks

A linear relative risk model was fit to the summarized data from the Louisville cohort used in this analysis (Table 2).[2] The assumed average cumulative exposure, the observed deaths from respiratory system cancer, and the expected deaths from respiratory cancer were used in a linear model to estimate the relative risk:

$$\text{Relative Risk} = \text{Observed}/\text{Expected} = a \cdot (1 + bd) \quad (3)$$

where d is a measure of cumulative exposure and a and b are parameters to be estimated. "Expected" was computed as the observed number of cases ("Observed") divided by the Standardized Mortality Ratio (SMR). Fitting to the human epidemiological data (Table 2) was accomplished via Poisson maximum likelihood techniques (Frome, 1983). The log-likelihood for the assumed Poisson distribution in a group having cumulative exposure d is expressed as:

$$LL = -\text{Expected} \cdot a \cdot (1 + bd) + \text{Observed} \cdot \ln(\text{Expected} \cdot a \cdot (1 + bd)). \quad (4)$$

This log-likelihood ignores terms that are constant for the data set (i.e., do not depend on the values of the parameters). The maximum total log-likelihood (summed over each exposure group) was obtained and retained for future computations, as HMLLs or HMLLp, corresponding to the unconstrained human log-likelihood for the standard and PBK metrics, respectively.

2.6. Human–animal comparison of chloroprene risk estimates

The current method was developed to test the null hypotheses that certain dose metrics would provide comparable risk estimates across species, specifically mice and humans. The approach was designed to determine if one or more of the selected dose metrics was consistent with the hypothesis that there was a common risk level (across species) associated with a dose or exposure pattern of interest. The alternative hypothesis, for a given dose metric, was that the risk at the dose of interest was not the same across species.

Preliminary analyses had suggested that the benchmark dose at the extra risk level of 0.10 (BMD10) from the multistage dose–response model was just slightly less than 1 ppm, so this air concentration was selected as a reasonable concentration for comparison of risk estimates across species. For the PBK metric comparison, a value of 0.00352 l mole of CD metabolized/g-lung/day was selected as the internal dose metric of interest as that was the value estimated with model simulations conducted at either 1 ppm via an occupational exposure scenario or with the adjusted continuous exposure equivalent of 0.33 ppm.

For the ppm metric (the standard metric), a single maximized log-likelihood was determined, the unconstrained animal maximum log-likelihood for the standard metric (AMLLs) (Fig. 3). For the PBK metric, the maximum log-likelihood (AMLLp) was computed in exactly the same manner, but using the PBK metric values as the dose inputs (Table 1). Correspondingly, calculation of human relative risks was conducted by fitting the relative risk model (Eq. (3)) to the epidemiology data to define the dose–response relationship using both the standard metric (with maximum likelihood HMLLs) and the PBK metric (yielding HMLLp). Using the animal and human log-likelihood estimates, unconstrained joint log-likelihoods of observing both the animal bioassay results and the epidemiological results were computed. The joint log-likelihoods were defined as "Unconstrained" meaning that the human and animal results were computed independently of one another. The computed unconstrained joint log-likelihoods (UMLLs and UMLLp) were determined based on the animal and human maximized log-likelihoods:

$$\text{UMLLs} = \text{AMLLs} + \text{HMLLs} \quad (5)$$

$$\text{UMLLp} = \text{AMLLp} + \text{HMLLp} \quad (6)$$

i.e., the metric-specific summation of the corresponding animal and human maximized log-likelihoods.

Constrained log-likelihoods were also calculated based on the null hypothesis that the animal bioassay data and the epidemiology data would provide the same estimate of risk at the dose of interest (1 ppm or 0.00352 l mole of CD metabolized/g-lung/day, depending on the metric under consideration). A joint log-likelihood for the combined human and animal results was calculated, under the assumption of equal risks at the dose of interest. If this constrained joint log-likelihood was sufficiently close to (by a formal statistical test) the unconstrained joint log-likelihood, then the null hypothesis of equal risks at those dose values was accepted.

The constrained maximum likelihood of interest was computed by examining values of b in the relative risk model (Eq. (3)), within a range of b values extending from 0 to an upper limit sufficient (by visual inspection) to guarantee that the maximum joint constrained log-likelihood was attained. For a selected value of b, the value of a in Eq. (3) was derived that maximized the human log-likelihood. In addition, for any selected value of b, a lifetime extra risk was calculated using the life table method used by EPA and others (Federal Register, 2004; USEPA, 2002, 2011) (Appendix A). The reference population for the life table calculations was the entire US population with rates from 2008 for all causes and respiratory system cancers (CDC, 2011). Risk was computed up through age 85. The lifetime human extra risk (HER) for a selected constant exposure level (dose-of-interest, or DOI) was computed using the life table approach with the various estimates of b; it was referred to as the HER(DOI).

Given the HER(DOI) value defined above, the multistage model was fit to the animal data with an added constraint, i.e., that the animal extra risk at the DOI, AER(DOI), equals the HER(DOI). The source code for the BMDS multistage model was modified (code supplied by the authors on request) to allow for such constrained optimization; it is not possible to do it with the BMDS models as they are distributed. The modification automates the following calculations. If AER(DOI) is set equal to HER(DOI), then the multistage fit to the animal data can be maximized under that constraint:

$$\begin{aligned} \text{HER}(\text{DOI}) = \text{AER}(\text{DOI}) &= [P(\text{DOI}) - P(0)]/[1 - P(0)] \\ &= 1 - e^{-(q_1 \text{DOI} + q_2 \text{DOI}^2)} \end{aligned} \quad (7)$$

where the second equality follows from the form of the multistage model equation (Eq. (2)). Solving for q_1, results in the following equation.

$$q_1 = -\ln(1 - \text{AER}(\text{DOI})) - q_2 \text{DOI}^2)/\text{DOI} \quad (8)$$

Consequently, when AER(DOI) is fixed at a value, HER(DOI), the optimization for estimating the maximum (constrained) likelihood

[2] Even though the individual data for this cohort were available to the authors, we have used the summary data in order to demonstrate how this approach can be implemented with data that are commonly available when using epidemiological study reports for risk assessment. If we had used the individual data, we could, for example, have used a Cox proportional hazards model to better control for other variables, like age.

from the multistage model can be accomplished by varying q_0 and q_2. (i.e., all the parameters other than q_1) and then computing q_1 as shown. For the current investigation, a 2nd degree multistage model was the highest polynomial degree needed. The same assumptions would apply for a polynomial degree greater than 2.

The two log-likelihood components, human and mouse, were then summed:

$$CMLLx(b) = HMLLx(b) + AMLLx(b); \quad (9)$$

indicating the dependence on the choice of b. The value of "x" in Eq. (9) was either s (for the standard, ppm metric) or p (for the PBK metric), just as for the unconstrained likelihood calculations. The full range of allowable b values was examined to determine a maximum for CMLLx(b); that maximum was the maximum constrained log-likelihood, CMLLx.

A likelihood ratio test was used to test the null hypothesis that the constraint of equal risks at DOI was true. The test statistics were:

$$2 \cdot (UMLLx - CMLLx) \quad (10)$$

(twice the differences in the log-likelihoods, x = s or p). There is one degree of freedom associated with the chi-squared distribution that approximates the distribution of those test statistics (Eq. (8) demonstrates there is one less parameter to be estimated, i.e., q_1, when the constraint of HER(DOI) = AER(DOI) is in effect, that is, when the null hypothesis is true). Larger differences in the maximized likelihoods yield larger values of the test statistic and therefore smaller p-values (i.e., probabilities of being in the tail of the chi-squared distribution to the right of the test statistic value). Small p-values (less than 0.05) were indicative of the null hypothesis being false.

2.7. Uncertainty analyses

An uncertainty analysis was conducted to evaluate the potential impact of the assignment of CD exposure concentrations (ppm) to the workers in the Louisville cohort. Esmen et al. (2007a) assigned nominal exposure levels to the members of the Louisville cohort, depending upon job class and calendar year. The uncertainty in the nominal levels was considered using "subtitles" for jobs within job class, the type of rotation among workers within those subtitles, and the deciles of the varying exposure levels associated with those subtitles. A Monte Carlo analysis was conducted, generating 3000 simulated human data sets, to evaluate the impact of exposure uncertainty. Each simulated human data set assigned different ppm exposure levels to each worker's work history, consistent with exposure uncertainty distributions defined in the Supplemental material; a detailed description of the approach used in the Monte Carlo for the assigning of exposures concentrations to the workers is provided in that Supplemental material.

Given the rules specified in the Supplemental material, 1500 alternative (simulated) exposure histories for the cohort members were generated and run through the OCMAP program (Marsh et al., 1998). The output of each of those runs was a set of dose–response data analogous to those shown in Table 2. The cut points for defining the exposure groups were the same as used in the original analysis (Marsh et al., 2007b) (second column of Table 2).

When considering the PBK metric for humans, the above procedure was used to generate another set of 1500 simulated data sets, but an additional step was included to represent the uncertainty between the ppm exposure level and the PBK dose metric value. That additional step utilized the posterior distributions of the PBK model parameters derived by Yang et al. (2012). Following the assignment of each ppm exposure level as described in the Supplemental material, a PBK metric value was generated by sampling from a lognormal distribution with (natural scale) mean and coefficient of variation equal to,

Table 3
Heuristic for comparing models via Bayesian Information Criteria (BIC) values.

DBIC[a]	Strength of evidence
< −10	Very strong evidence for model i
−10 to −6	Strong evidence for model i
−6 to −2	Positive evidence for model i
−2 to 2	Not much evidence either way
2 to 6	Positive evidence against model i
6 to 10	Strong evidence against model i
>10	Very strong evidence against model i

[a] DBIC = BIC(i) − BIC(j), where BIC(k) is the BIC associated with model k. Based on the categorization shown in Kass and Raftery (1995).

$$\begin{aligned} l &= 0.00373 \text{ ppm} \\ CV &= 0.74; \end{aligned} \quad (11)$$

respectively. Those values for l and coefficient of variation (CV) (the log-scale variance equals $\ln[1 + CV^2]$) were selected based on the following observations. The posterior distributions of the PBK model parameters (Yang et al., 2012) were sampled 500 times each for five exposure concentrations ranging from 0.016 to 160 ppm (by factors of 10)[3] and the associated PBK metric values (for the occupational exposure scenario) were computed for each sampling. As discussed elsewhere, the human ppm-to-PBK metric conversion is linear (for this range of ppm exposure levels); the factor of 0.00373 was associated with the average of the 2500 generated PBK metric values. Similarly, a CV of 0.74 was consistent with the variation observed across all those generated PBK metric values (conditional on the value of the mean).

The cut points on cumulative PBK metric values used to assign person years of observation to four exposure groups were those shown in Table 2 (second column) multiplied by 0.00352 (the conversion factor obtained when using PBK model parameter values equal to the means of each posterior distribution).

For each of the 3000 simulated data sets, the unconstrained and constrained maximization of the log-likelihoods was completed just as described in Section 2.5 above. For interpretation of the results of the uncertainty analysis the Bayesian Information Criteria (BICs) were used to evaluate the strength of the evidence for or against any given model. The BIC is defined as,

$$BIC = -2 \cdot MLL + \ln(n) \cdot parms; \quad (12)$$

where MLL, is the maximized log-likelihood, n is the number of observations, and parms is the number of parameters in the model. For the joint log-likelihoods (across mouse and human data sets) that we are analyzing here, n = 8 (four dose groups each for the mice and humans); parms = 5 for the unconstrained model (mouse and human data fit separately and independently) and parms = 4 for the constrained model (see Eq. (7) and associated text for a discussion of the reduction in the number of parameters under the constraint of equal risk at the DOI).

Lower values of the BIC indicate a better model. The BIC (like other information criteria) "rewards" a model for better fit (greater log-likelihood) but "penalizes" a model that uses more parameters to achieve a better fit. Put another way, the BIC rewards fit and parsimony.

A model comparison heuristic was introduced by Jeffreys (1961) and refined by Kass and Raftery (1995) (Table 3); it provides a categorization of the strength of the evidence for or against a given model, relative to another model. In our case, DBIC was defined with the unconstrained model as the referent, DBIC = BIC

[3] These exposure levels were those reported in Esmen et al. (2007a,b) as the nominal chloroprene levels for their exposure classes (see their Table 2).

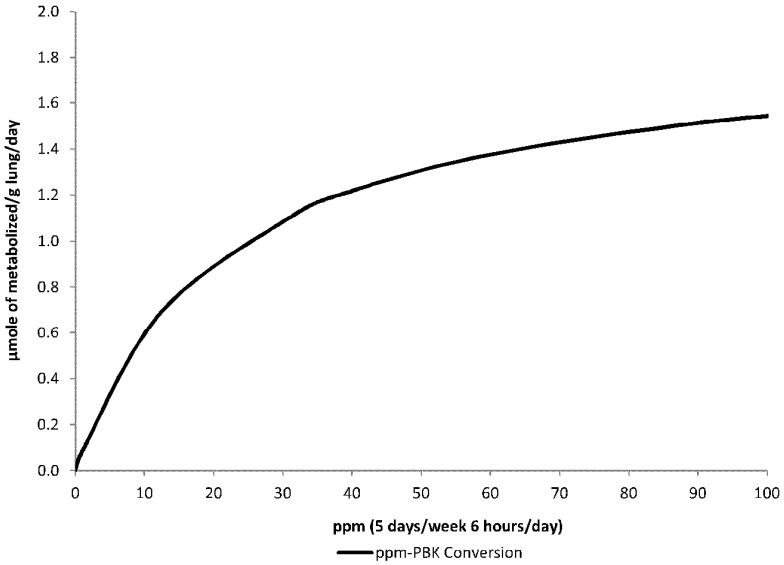

Fig. 2. Relationship between experimental exposure levels and PBK metric values; female mice.

(constrained) − BIC (unconstrained). Therefore, negative values of the DBIC favor the constrained model; positive values favor the unconstrained model. The results of the uncertainty analysis were summarized by tabulating the number of iterations of the simulations for which the constrained model falls in each of the evidence categories.

3. Results

The animal data set (Table 1) was not well described by the multistage model, when the doses were expressed in terms of the ppm exposure levels. The p-value for goodness-of-fit was 0.0046, a p-value indicating inadequate fit of the model to the data (p-values of greater than 0.10 are considered an adequate fit (USEPA, 2005)). The use of the PBK dose metric resulted in an adequate fit of the multistage model to the animal data (p-value = 0.44). Because of the saturation of metabolism in the lungs of female mice within the range of the experimental exposures (Fig. 2), the use of the internal PBK dose metric better correlated with the lung tumor incidence in the mouse than the external ppm dose metric. The PBK transformation was successful with respect to making differences in delivered dose accord with differences in response rates, when a multistage model represents the underlying carcinogenic process for the selected respiratory system cancer response.

The unconstrained, maximized log-likelihoods for the animal models were AMLLs = − 105.758 (for the standard, ppm metric) and AMLLp = − 101.049 (when using the PBK metric). The increase in the log-likelihood with use of the PBK metric is also indicative of a better fit, relative to use of the ppm exposure levels.

The human dose–response data (Table 2), were best fit by a relative risk model (Eq. (3)) with a slope (b) of zero and a = 0.74. The fact that b = 0 is consistent with the absence of a dose–response relationship between cumulative exposure and respiratory system cancer deaths in those workers.[4] This was true whether or not the dose was expressed in terms of ppm-years or (lmole/g lung/day)-years, at least partially because the PBK transformation in humans was linear for the relatively low exposure levels experienced by this cohort (Fig. 3). The maximized log-likelihood for the relative risk model with 0 slope was HMLLs = HMLLp = 849.396 (regardless of the dose metric used).

Therefore, the "base case," unconstrained maximized combined log-likelihoods were,

UMLLs ¼ 743:638 ð13Þ
UMLLp ¼ 748:347

for the ppm exposure metric and for the PBK metric, respectively (Table 4).

3.1. Human–animal comparison of chloroprene risk estimates

The constrained optimization considered the animal and human data simultaneously, and maximized the sum of the animal and human log-likelihoods subject to one constraint, that the extra risk for the two fitted models be the same at the DOI. For the ppm exposure metric, the maximum constrained log-likelihood was attained when the relative risk slope was b = 0.0017 (per ppm-year). For that slope estimate, HMLLs(b) = 848.345, AMLLs(b) = − 118.063 and therefore CMLLs = 730.282 (Table 4). The comparison of the constrained maximum log-likelihood to the unconstrained maximum log-likelihood (UMLLs = 743.638) indicates a statistically significant difference (p-value = 2 × 10^{-7}). This indicates that the animal- and human-based risks at 1 ppm are not the same (i.e., rejection of the null hypothesis). For the PBK metric, the DOI was set to 0.00352 lmole of CD metabolized/g lung/day, the PBK dose-metric that corresponds to an occupational exposure of 1 ppm. Under the constraint that the animal extra risk was the same as the human extra risk at that dose, the maximum constrained log-likelihood was attained when the relative risk slope was b = 0.125 (per (lmole/g lung/day) – years), and HMLLp(b) = 848.676, AMLLp(b) = − 101.254, and therefore CMLLp = 747.422.

The PBK metric provides consistent cross-species low-dose risk estimates (the p-value for the test of the null hypothesis equals 0.17). The null hypothesis of equal risk at the PBK dose of 0.00352 lmole/g lung/day would not be rejected at the typical

[4] For the relative risk model, the slope was constrained to be non-negative. No evaluation was conducted to determine if negative values for the slope were better than zero. It was considered implausible that chloroprene exposure would reduce respiratory cancer risk.

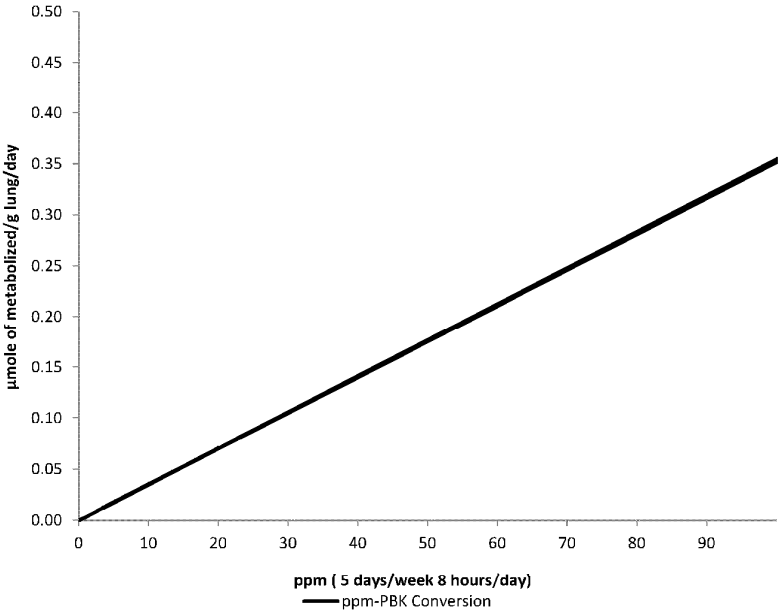

Fig. 3. Relationship between occupational exposure levels and PBK metric values; humans.

0.05 level of significance. Not only did the PBK transformation of doses result in a substantially improved model fit to the animal data, it also reconciled cross-species predictions of risk estimates for low doses.

Table 4
Unconstrained and constrained maximized log-likelihoods.

Dose-metric	Animal	Human	Combined
Unconstrained			
ppm metric	└ 105.758	849.396	743.638
PBK metric	└ 101.049	849.396	748.347
Constrained			
ppm metric	└ 118.063	848.345	730.282
PBK metric	└ 101.254	848.676	747.422

Naturally, the unconstrained fit to the animal data provided the best fit. Although the constrained fit to the animal data (where the animal risk at the DOI was constrained to equal the human risk at the DOI) was not as good as the unconstrained fit, the predicted probabilities of response were still well within the (1 SE) error bars associated with the observed response rates (Fig. 4). Importantly, the constrained curve had a less steep slope at low doses, which conforms better to the (at most) shallow slope for the human dose–response. The achievement of a shallow low-dose slope with enough curvature to match the observations at the higher

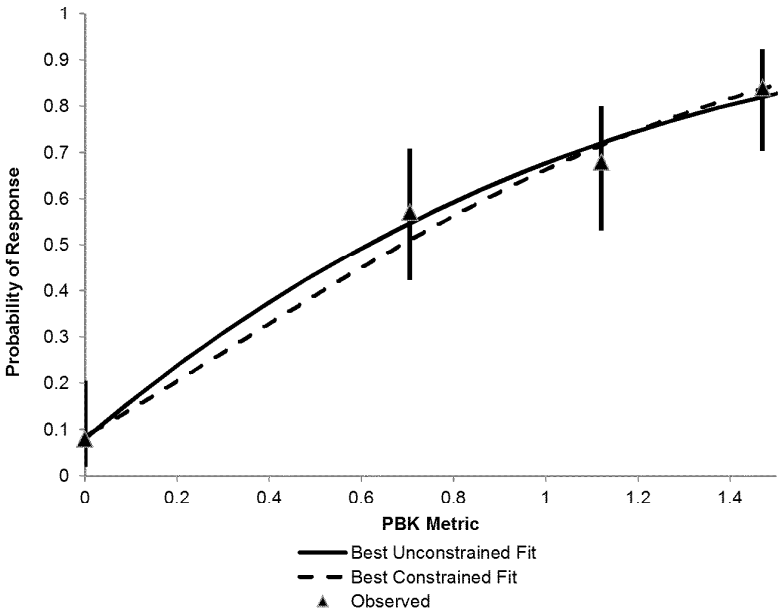

Fig. 4. Comparison of best unconstrained and constrained fits to animal data.

Table 5
Evidence for and against the constrained model, by exposure metric.[b]

DBIC[a]	Strength of evidence	No. simulated cohort data sets in each category	
		ppm metric	PBK metric
< −10	Very strong evidence for constrained model	0	736
−10 to −6	Strong evidence for constrained model	1	284
−6 to −2	Positive evidence for constrained model	16	236
−2 to 2	Not much evidence either way	46	162
2 to 6	Positive evidence against constrained model	131	63
6 to 10	Strong evidence against constrained model	259	13
>10	Very strong evidence against constrained model	1047	6

[a] DBIC = BIC(constrained) − BIC(unconstrained).
[b] Each simulated cohort data set was subject to constrained and unconstrained maximum likelihood estimation. The final two columns shows the number (out of 1500) of those data sets that had different degrees of support for or against the constrained model, depending on the choice of exposure metric.

experimental exposure levels is what allows for a consistent risk estimate at the DOI.

3.2. Uncertainty analyses

Uncertainty in estimated human exposures had an interesting effect on the comparison of the constrained and unconstrained models (Table 5). For the models applied to the ppm metric, exposure uncertainty implied a range of estimates that predominantly did not support the constrained model; all but 63 (of 1500) simulated exposure runs demonstrated evidence against the constrained model and, therefore, against the hypothesis that mice and humans have equal risk at 1 ppm (when risks were equilibrated on the basis of ppm exposure levels). When the PBK metric was used, there was a notable shift to values that favor the constrained model. A total of 1256 runs demonstrated evidence for the constrained model (nearly half were consistent with very strong evidence in favor of the constrained model and, therefore, for the equality of animal and human risks at low doses). The ability to eliminate one parameter in the optimization was of key importance, especially when the log-likelihoods for the constrained and the unconstrained models were similar. The DBIC for the base case (no uncertainty) constrained model using the PBK metric was −0.23, i.e., little or no evidence for or against it relative to the unconstrained model. This result is consistent with the failure to reject the null hypothesis of no difference in risk across species at the PBK dose of interest.

4. Discussion and conclusions

The analysis described here presents a new method to compare and test risk predictions across species for lifetime extra cancer risk. It requires that specific methods be applied as appropriate to the type of data available, but all having the goal of predicting lifetime extra cancer risk. Thus, for the epidemiological data, relative risk Poisson modeling linked to life-table calculations yields the necessary risk estimates. For the animal bioassay data, multistage modeling is applied. Those two sides of the analysis were subject to a formal statistical evaluation that addressed hypotheses of interest using likelihood procedures.

This approach allows for reproducible and consistent comparisons of experimental and/or observational data that are commonly used for risk assessment purposes. In the specific case of CD, the results of applying this approach indicate that external, concentration-based estimates of exposure to CD are not the appropriate dose metric for estimating comparable risk estimates across species. Even when accounting for one of the largest uncertainties associated with the use of epidemiological data for dose–response assessment, i.e., reconstructing occupational human exposure levels, there was little or no statistical support for the hypothesis that human and animal low-dose risks are equivalent when exposure was expressed in terms of ppm air concentration. Conversely, the use of the PBK metric, daily amount of CD metabolized at the target per gram of tissue, in the dose–response models provided better fit of the models to the data due to the ability of the PBK metric to account for the cross-species metabolic differences. It also resulted in comparable risk estimates across species at the dose of interest, and more generally, at all doses less than or equal to the dose of interest.

The evaluation of the animal and human data using the PBK metric provided cancer slope factors between 2.9×10^{-5} and 1.4×10^{-2} per ppm, with the maximum-likelihood estimate of 6.7×10^{-3} per ppm. The human equivalent cancer slope factor estimated based on the incidence of lung tumors in female mice (the most sensitive sex and species) reported in the EPA Toxicological Review (2010) is 6.5×10^{-1} per ppm (adjusted for exposure 6/24 h and 5/7 days). This slope factor is approximately 100 times greater than the maximum-likelihood estimate determined with the current approach.

While the current adjustment for pharmacokinetic differences across species results in comparable risk estimates, there are

Table 6
Evaluation of the presence of pharmacodynamic differences across species.

Relative pharmacodynamic sensitivity	Mouse PBK metric value (lmole of CD metabolized/g lung/day)	Mouse metric/ human metric	Test of equality of risks at the specified PBK doses (p-value)[a]
Humans more sensitive	0.0845	24	0.001
	0.0282	8	0.029
	0.00845	2.4	0.056
Humans equally sensitive	0.00352	1	0.17
Humans less sensitive	0.00282	0.8	0.22
	0.000845	0.24	0.54

[a] P-values are from the test of various null hypotheses, i.e., that the risk at the specified mouse metric values is equal to the risk at the human PBK metric value of 0.00352 lmole/g lung/day (the constrained maximum likelihood calculations). The alternative hypotheses are that there is no such constraint; the mouse and human models are independent so do not necessarily predict equivalent risks at the specified doses.

additional factors that could be considered to further refine the evaluation. These could include species-specific differences in detoxification and pharmacodynamics.

In the case of CD, the data are not currently available to estimate or model the magnitude of species differences in such additional factors. However, the current analysis approach provides evidence that, if and when such data become available they will demonstrate that humans are equally or less sensitive, but not more sensitive than mice, at the low levels of CD exposure investigated. That "working hypothesis" results from the analysis results shown in Table 6. If one assumes that risk is equal when the human PBK metric value is 0.00352 Ì mole CD metabolized/g-lung/day and the mouse metric value is at different levels (greater or less than 0.00352), equivalence of risk was only supported (having p-values greater than 0.05) when the proposed equivalent-risk mouse dose was less than or equal to about 2.4 times the human dose of 0.00352. The working hypothesis of lower human low-dose risk still remains to be tested formally with data specifically obtained and appropriate for that purpose. Until then, the results of the current analyses suggest that humans are equally or less sensitive than mice to equivalent low-dose CD exposures.

Conflict of interest

B.C. Allen: Sub-contract to ENVIRON International Corporation and The Hamner Institutes for Health Sciences. C. Van Landingham: Contract to ENVIRON International Corporation. Y. Yang: Personal fees from International Institute of Synthetic Rubber Produces, Inc. (IISRP). A.O. Youk: Grants from International Institute of Synthetic Rubber Produces, Inc. (IISRP) and personal fees from DuPont Chemical Company. G.M. Marsh: Grants from International Institute of Synthetic Rubber Produces, Inc. (IISRP), personal fees from DuPont Chemical Company. N. Esmen: Nothing to disclose. P.R. Gentry: Contract to ENVIRON International Corporation. H.J. Clewell III: Personal fees from International Institute of Synthetic Rubber Produces, Inc. (IISRP). M.W. Himmelstein: Nothing to disclose.

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Appendix A. Formulae for calculating extra risk using a life-table method

The probability of disease occurrence (incidence or mortality) between ages x_1 and x_2 may be expressed as:

$$p(0) = \int_{x_1}^{x_2} h(x)S(x)dx \qquad (A1)$$

where S(x) is the probability of survival to age x given survival to age x_1 and h(x) is the instantaneous hazard of disease occurrence at age x. This integral can be approximated by a sum:

$$p(0) = \sum_{i=1} p(i)S(i) \qquad (A2)$$

where the age interval $[x_1, x_2]$ has been divided into n subintervals with the ith subinterval having width D(i), i = 1 „ . . . , n, p(i), representing the probability of disease occurrence in the ith age interval, is calculated as:

$$p(i) = q_c(i)D(i); \qquad (A3)$$

and S(i), representing the probability of surviving to the beginning of the ith age interval given survival to age x_1, is calculated as S(1) = 1 and:

$$S(i) = \prod_{j=1} \exp\left(-q_a(j)D(j)\right) = \exp\left[-\sum_{j=1} q_a(j)D(j)\right]; \quad i > 1 \qquad (A4)$$

where $q_c(i)$ and $q_a(i)$ are the cause-specific rate of occurrence and all-cause death rates for the ith age interval obtained from standard rate tables. An alternative to (Eq. (A4)) is given by:

$$S(i) = \prod_{j=1} \left[1 - q_a(j)D(j)\right]; \quad i > 1; \qquad (A5)$$

which encompasses slightly different interpretations of the standard rates. These 2 expressions generally agree closely.

If the subintervals correspond to individual years, (Eqs. (A2) and (A4)) take on the simplified forms:

$$p(0) = \sum_{i=x_1} q_c(i)S(i); \qquad (A6)$$

and:

$$S(i) = \prod_{j=x_1} \exp\left(-q_a(j)\right) = \exp\left[-\sum_{j=x_1} q_a(j)\right] \qquad (A7)$$

Once the background rates q_c and q_a are selected, these equations completely determine p(0). These same formulae are used to calculate the probability of response, p(D), from a particular exposure pattern, D, by replacing the rates q_c and q_a by the appropriate modification that accounts for the model-predicted effect of exposure on these rates. The appropriate modifications depend upon the form of the dose–response model estimated from the epidemiologic data, and the assumed exposure pattern. If the dose–response model predicts relative risk as a function of some exposure metric, then:

$$q_c(i) \text{ is replaced by } q_c(i)R(i) \qquad (A8)$$

and:

$$q_a(i) \text{ is replaced by } q_a(i) - q_c(i)D(i) + R(i)q_c(i)D(i) = q_a(i)D(i) + q_c(i)D(i)R(i) - 1]; \qquad (A9)$$

where R(i) is the relative risk predicted by the dose-response model, i.e., R(i) = 1 + b * D(i), where D(i) is the cumulative dose at age i from exposure pattern D. The latter replacement involves subtracting from the total death rate the background death rate from the disease of interest, and adding back this contribution adjusted by the effect of exposure.

Once p(0) and p(D) have been calculated, the extra risk from exposure pattern D is computed as:

$$[p(D) - p(0)]/[1 - p(0)] \qquad (A10)$$

This extra risk is what will be compared with the animal-based extra risk estimate.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2014.07.001.

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